STEDMAN'S Medical Dictionary

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au·to·ca·tal·y·sis (aw'tō-kă-tal'i-sis). A reaction in which one or more of the products formed acts to catalyze the reaction; beginning slowly, the rate of such a reaction rapidly increases. Cf. chain *reaction*. SYN autoactivation.

au·to·cat·a·lyt·ic (aw'tō-kat-ă-lit'ik). Relating to autocatalysis.

au·to·cath·e·ter·i·za·tion, au·to·cath·e·ter·ism (aw'tō-kath-ĕ-ter-i-zā'shŭn, -kath'ĕ-ter-izm). Passage of a catheter by the patient.

au·toch·thon·ous (aw-tok'thon-ŭs). **1.** Native to the place inhabited; aboriginal. **2.** Originating in the place where found; said of a disease originating in the part of the body where found, or of a disease acquired in the place where the patient is. [auto- + G. *chthon,* land, ground, country]

au·toc·la·sis, au·to·cla·sia (aw-tok'lă-sis, aw-tō-klā'zē-ă). **1.** A breaking up or rupturing from intrinsic or internal causes. **2.** Progressive immunologically induced tissue destruction. [auto- + G. *klasis,* breaking]

au·to·clave (aw'tō-klāv). **1.** An apparatus for sterilization by steam under pressure; it consists of a strong closed boiler containing a small quantity of water and, in a wire basket, the articles to be sterilized. **2.** To sterilize in an autoclave. [auto- + L. *clavis,* a key, in the sense of self-locking]

au·to·coid (aw'tō-koyd). A chemical substance produced by one type of cell that affects the function of different types of cells in the same region, thus functioning as a local hormone or messenger. SYN autacoid substance, autacoid. [G. *autos,* self, + *eidos,* form]

au·to·crine (aw'tō-krin). Denoting self-stimulation through cellular production of a factor and a specific receptor for it. [auto- + G. *krinō,* to separate]

au·to·cys·to·plas·ty (aw-tō-sis'tō-plas-tē). SYN autoaugmentation. [auto- + G. *kystis,* bladder, + *plastos,* formed]

au·to·cy·to·ly·sin (aw'tō-sī-tol'i-sin). SYN autolysin.

au·to·cy·tol·y·sis (aw'tō-sī-tol'i-sis). SYN autolysis.

au·to·cy·to·tox·in (aw'tō-sī-tō-toks'in). A cytotoxic autoantibody.

au·to·der·mic (aw-tō-der'mik). Relating to one's own skin; denoting especially an autodermic graft or dermatoautoplasty. [auto- + G. *derma,* skin]

au·to·di·ges·tion (aw'tō-dī-jes'chŭn). SYN autolysis.

au·to·dip·loid (aw-tō-dip'loyd). SEE autoploid.

au·to·drain·age (aw-tō-drān'ij). Drainage into contiguous tissues.

au·to·ech·o·la·lia (aw'tō-ek-ō-lā'lē-ă). A morbid repetition of another person's or one's own words. [auto- + echolalia]

au·to·e·rot·ic (aw'tō-ĕ-rot'ik). Pertaining to autoerotism.

au·to·e·rot·i·cism (aw'tō-ĕ-rot'i-sizm). Sexual arousal or gratification using one's own body, as in masturbation. SYN autoerotism. [auto- + G. *erōtikos,* relating to love]

au·to·er·o·tism (aw-tō-ăr'ō-tizm). SYN autoeroticism. [auto- + G. *erōtikos,* relating to love]

au·to·flu·o·ro·scope (aw-tō-flōr'ō-skōp). A type of scintillation camera consisting of a matrix of individual sodium iodide crystals, each with its separate light pipe and photomultiplier tube; used for radioisotope imaging procedures.

au·tog·a·mous (aw-tog'ă-mŭs). Relating to or characterized by autogamy.

au·tog·a·my (aw-tog'ă-mē). A form of self-fertilization in which fission of the cell nucleus occurs without division of the cell, the two pronuclei so formed reuniting to form the synkaryon; in other cases, the cell body also divides, but the two daughter cells immediately conjugate. SYN automixis. [auto- + G. *gamos,* marriage]

au·to·gen·e·sis (aw-tō-jen'ĕ-sis). **1.** The origin of living matter within the organism itself. **2.** In bacteriology, the process by which vaccine is made from bacteria obtained from the patient's own body. [auto- + G. *genesis,* production]

au·to·ge·net·ic, au·to·gen·ic (aw'tō-jĕ-net'ik, jen'ik). Relating to autogenesis. SYN autogenous (1).

au·tog·e·nous (aw-toj'ĕ-nŭs). **1.** SYN autogenetic, autologous. **2.** Originating within the body, applied to vaccines prepared from bacteria or other cells obtained from the affected person. Cf. endogenous. [G. *autogenēs,* self-produced]

au·tog·no·sis (aw-tog-nō'sis). Recognition of one's own character, tendencies, and peculiarities. SYN self-knowledge. [auto- + G. *gnōsis,* knowledge]

au·to·graft (aw'tō-graft). Tissue or organ transferred into a new position in the body of the same individual. SYN autogeneic graft, autologous graft, autoplastic graft, autotransplant. [auto- + A.S. *graef*]

au·to·graft·ing (aw-tō-graft'ing). SYN autotransplantation.

au·to·gram (aw'tō-gram). A wheal-like lesion on the skin following pressure by a blunt instrument or by stroking. [auto- + G. *gramma,* something written]

au·tog·ra·phism (aw-tog'ră-fizm). SYN dermatographism.

au·to·hem·ag·glu·ti·na·tion (aw'tō-hē'mă-gloo-ti-nā'shŭn). Autoagglutination of autologous erythrocytes.

au·to·he·mo·ly·sin (aw'tō-hē-mol'i-sin). An autoantibody that causes lysis of erythrocytes in the presence of complement.

au·to·he·mol·y·sis (aw'tō-hē-mol'i-sis). Hemolysis occurring in certain diseases as a result of an autohemolysin.

au·to·hex·a·ploid (aw-tō-heks'ă-ployd). SEE autoploid.

au·to·hyp·no·sis (aw'tō-hip-nō'sis). Self-induced hypnosis, accomplished by concentrating on self-absorbing thought or on the idea of being hypnotized. SYN autohypnotism, idiohypnotism.

au·to·hyp·not·ic (aw'tō-hip-not'ik). Relating to autohypnosis.

au·to·hyp·no·tism (aw-tō-hip'nō-tizm). SYN autohypnosis.

au·to·im·mune (aw-tō-i-mūn'). Cells and/or antibodies arising from and directed against the individual's own tissues, as in autoimmune disease.

au·to·im·mu·ni·ty (aw'tō-i-mū'ni-tē). **1.** In immunology, the condition in which one's own tissues are subject to deleterious effects of the immune system, as in autoallergy and in autoimmune disease; specific humoral or cell-mediated immune response against the body's own tissues. SYN autoallergy. **2.** Literally, the condition in which "self" is exempt.

au·to·im·mu·ni·za·tion (aw'tō-im'ū-ni-zā'shŭn). Induction of autoimmunity.

au·to·im·mu·no·cy·to·pe·nia (aw-tō-im'oo-nō-sī-tō-pē'nē-ă). Anemia, thrombocytopenia, and leukopenia resulting from cytotoxic autoimmune reactions.

au·to·in·fec·tion (aw'tō-in-fek'shŭn). **1.** Reinfection by microbes or parasitic organisms that have already passed through an infective cycle. **2.** Self-infection by direct contagion as with pinworm (*Enterobius vermicularis*) eggs passed in the infectious state and transmitted by fingernails (anal-oral route). SYN autoreinfection, self-infection.

au·to·in·fu·sion (aw'tō-in-fū'shŭn). Forcing the blood from the extremities or other areas such as the spleen, as by the application of a bandage or pressure device, to raise the blood pressure and fill the vessels in the vital centers; resorted to after excessive loss of blood or other body fluids. Cf. autotransfusion.

au·to·in·oc·u·la·ble (aw'tō-in-ok'ū-lă-bl). Susceptible to autoinoculation.

au·to·in·oc·u·la·tion (aw'tō-in-ok-ū-lā'shŭn). A secondary infection originating from a focus of infection already present in the body.

au·to·in·tox·i·cant (aw'tō-in-toks'i-kant). An endogenous toxic agent that causes autointoxication. SYN autotoxin.

au·to·in·tox·i·ca·tion (aw'tō-in-toks-i-kā'shŭn). A disorder resulting from absorption of the waste products of metabolism, decomposed matter from the intestine, or the products of dead and infected tissue as in gangrene. SYN autotoxicosis, endogenic toxicosis, enterotoxication, enterotoxism, intestinal intoxication, self-poisoning.

au·to·i·sol·y·sin (aw'tō-ī-sol'i-sin). An antibody that in the presence of complement causes lysis of cells in the individual in whose body the lysin is formed, as well as in others of the same species.

au·to·ker·a·to·plas·ty (aw-tō-ker'ă-tō-plas-tē). Grafting of cor-

especially with reference to such changes associated with inflammations and certain types of malignant neoplasms.

epituberculous i., an i. superimposed upon a tuberculous lesion.

fatty i., abnormal accumulation of fat droplets in the cytoplasm of cells, particularly of fat derived from outside the cells. SEE ALSO *fatty degeneration.*

gelatinous i., SYN gray i.

gray i., a term sometimes used for the relatively rapidly formed, semisolid, gray or gray-white exudate (chiefly necrotic cells and remnants of tissue, and macrophages) resulting from unusually acute, overwhelming, diffuse tuberculous infection in the lung. SYN gelatinous i.

lipomatous i., nonencapsulated adipose tissue forming a lipomalike mass, usually in the cardiac interatrial septum where it may cause arrhythmia and sudden death. SYN lipomatous hypertrophy.

paraneural i., SYN perineural i.

perineural i., i. adjacent to or along a nerve. SYN paraneural i.

in·fin·i·ty (in-fin'i-tē). SYN infinite *distance.*

in·firm (in-ferm'). Weak or feeble because of old age or disease. [L. *in-firmus,* fr. *in-* neg. + *firmus,* strong]

in·fir·ma·ry (in-fer'mă-rē). A clinic or small hospital, especially in a school or college. [L. *infirmarium;* see infirm]

in·fir·mi·ty (in-fer'mi-tē). A weakness; an abnormal, more or less disabling, condition of mind or body. [see infirm]

in·flam·ma·ble (in-flam'ă-bl). SYN flammable. [L. *in-,* intensive, + *flamma,* flame]

in·flam·ma·tion (in-flă-mā'shŭn). A fundamental pathologic process consisting of a dynamic complex of cytologic and chemical reactions that occur in the affected blood vessels and adjacent tissues in response to an injury or abnormal stimulation caused by a physical, chemical, or biologic agent, including: 1) the local reactions and resulting morphologic changes, 2) the destruction or removal of the injurious material, 3) the responses that lead to repair and healing. The so-called "cardinal signs" of i. are: *rubor,* redness; *calor,* heat (or warmth); *tumor,* swelling; and *dolor,* pain; a fifth sign, *functio laesa,* inhibited or lost function, is sometimes added. All of the signs may be observed in certain instances, but no one of them is necessarily always present. [L. *inflammo,* pp. *-atus,* fr. *in,* in, + *flamma,* flame]

active i., SYN acute i.

acute i., any i. that has a fairly rapid onset, quickly becomes severe, and is usually manifested for only a few days, but which may persist for even a few weeks; characterized histologically by edema, hyperemia, and inflitrates of polymorphonuclear leukocytes. SYN active i.

adhesive i., i. in which the amount of fibrin in the exudate is sufficient to result in a slight or moderate degree of adherence of adjacent tissues, as in healing by first intention.

allergic i., SEE allergic *reaction.*

alterative i., a local reaction to injury, occasionally observed in the walls of blood vessels and in parenchymal cells of various organs in reacting to certain chemicals, viruses, and other intracellular agents; the response is characterized by degenerative changes in the cytoplasm and nucleus, frequently resulting in necrosis, but exudation (if any) is ordinarily observed only in the wall of the affected vessel, or in the interstices immediately adjacent to the affected vessel or parenchymal cells. SYN degenerative i.

atrophic i., a form of chronic i. or repeated episodes of acute i. in which the continued or recurrent proliferation of fibroblasts results in the formation of fibrous tissue that eventually contracts and leads to compression and atrophy of parenchymal tissue. SYN fibroid i.

catarrhal i., obsolete term for an inflammatory process that is most frequent in the respiratory tract, but may occur in any mucous membrane, and is characterized by hyperemia of the mucosal vessels, edema of the interstitial tissue, enlargement of the secretory epithelial cells (which proliferate and form conspicuous globules of mucus), and an irregular layer of viscous, mucinous material on the surface; as exudation progresses, variable numbers of neutrophils migrate into the affected tissue and are included in the exudate, along with fragments of degenerated and necrotic epithelial cells; such an i. may frequently become mucopurulent.

chronic i., an i. that may begin with a relatively rapid onset or in a slow, insidious, and even unnoticed manner, and which tends to persist for several weeks, months, or years and has a vague and indefinite termination; occurs when the injuring agent (or products resulting from its presence) persists in the lesion, and the host's tissues respond in a manner (or to a degree) that is not sufficient to overcome completely the continuing effects of the injuring agent; characterized histopathologically by infiltrates of lymphocytes, plasma cells, and histiocytes; fibrosis; and granuloma formation.

chronic active i., the coexistence of chronic i. and superimposed acute i.

degenerative i., SYN alterative i.

exudative i., i. in which the conspicuous or distinguishing feature is an exudate, which may be chiefly serous, serofibrinous, fibrinous, or mucous (e.g., relatively few cells are present), or may be characterized by relatively large numbers of neutrophils, eosinophils, lymphocytes, monocytes, or plasma cells, frequently with one or two types being predominant; it occurs not only as a separate and distinct pathologic process, but also frequently as a part of certain granulomatous i.'s.

fibrinopurulent i., a purulent i. in which the exudate contains an unusually large amount of fibrin; also, a fibrinous or serofibrinous i. in which the accumulation of large numbers of polymorphonuclear leukocytes results in liquefactive necrosis of tissue and the formation of pus with a relatively large quantity of fibrin.

fibrinous i., an exudative i. in which there is a disproportionately large amount of fibrin.

fibroid i., SYN atrophic i.

granulomatous i., a form of proliferative i. SEE ALSO granuloma.

hyperplastic i., SYN proliferative i.

immune i., SEE allergic *reaction.*

interstitial i., i. in which the inflammatory reaction occurs chiefly in the supportive fibrous connective tissue or stroma of an organ.

necrotic i., necrotizing i., usually an acute inflammatory reaction in which the predominant histologic change is fairly rapid necrosis that occurs diffusely or extensively in relatively large foci throughout the affected tissue, frequently with only little or no evidence of cells in the exudate.

productive i., a vague term ordinarily used with reference to proliferative i., with or without an exudate; also sometimes used to indicate any i. in which grossly visible exudate is formed.

proliferative i., an inflammatory reaction in which the distinguishing feature is an actual increase in the number of tissue cells, especially the reticuloendothelial macrophages, in contrast to cells exuded from blood vessels; in addition, exudates of various types are likely to be observed in granulomas and other forms of proliferative i., but the latter may occur without an exudate being formed (as in certain infections caused by virus). SYN hyperplastic i.

pseudomembranous i., a form of exudative i. that involves mucous and serous membranes; relatively large quantities of fibrin in the exudate result in a rather tenacious membrane-like covering that is fairly adherent to the underlying acutely inflamed tissue; the pseudomembrane usually contains (in addition to the dense network of fibrin) varying quantities of plasma protein, degenerated and necrotic elements from the affected tissue, polymorphonuclear leukocytes, bacteria, etc.

purulent i., an acute exudative i. in which the accumulation of polymorphonuclear leukocytes is sufficiently great that their enzymes cause liquefaction of the affected tissues, focally or diffusely; the purulent exudate is frequently termed pus, and consists of plasma and its constituents, end products of the enzymatic digestion of tissue, degenerated and necrotic cells and their debris, polymorphonuclear leukocytes and other white blood cells, the causal agent of the i., etc. SYN suppurative i.

sclerosing i., i. leading to extensive formation of fibrous and scar tissue.

serofibrinous i., i. in which the exudate consists chiefly of serous fluid with an unusually large proportion of fibrin.

serous i., an exudative i. in which the exudate is predominantly fluid (e.g., exuded from the blood vessels), with the protein, electrolytes, and other material contained therein; relatively few (if any) cells are observed.

subacute i., an i. that is intermediate in duration between that of an acute i. and that of a chronic i., usually persisting longer than 3 or 4 weeks.

suppurative i., SYN purulent i.

in·flam·ma·to·ry (in-flam'ă-tōr-ē). Pertaining to, characterized by, causing, resulting from, or becoming affected by inflammation.

in·fla·tion (in-flā'shŭn). Distention by a fluid or gas. [L. *inflatio*, fr. *in-flo*, pp. *-flatus*, to blow into, inflate]

in·fla·tor (in-flā'ter, -tŏr). An instrument for injecting air.

in·flec·tion, in·flex·ion (in-flek'shŭn). **1.** An inward bending. **2.** Obsolete term for diffraction. [L. *in-flecto*, pp. *-flexus*, to bend]

in·flu·en·za (in-floo-en'ză). An acute infectious respiratory disease, caused by influenza viruses, which are in the family Orthomyxoviridae, in which the inhaled virus attacks the respiratory epithelial cells of susceptible persons and produces a catarrhal inflammation; characterized by sudden onset, chills, fever of short duration (3–4 days), severe prostration, headache, muscle aches, and a cough that usually is dry and may be followed by secondary bacterial infections that can last up to 10 days. The disease commonly occurs in epidemics, sometimes in pandemics, which develop quickly and spread rapidly; mortality rate is usually low, but may be high in cases with secondary bacterial pneumonia, particularly in the elderly and those with underlying debilitating diseases; strain-specific immunity develops, but mutations in the virus are frequent, and the immunity usually does not affect antigenically different strains. SYN flu, grip (1), grippe. [It. influence (of planets or stars), fr. L. *influentia*, fr. *in-fluo*, to flow in]

i. A, the most common type of influenza. These strains have a high propensity for antigenic change resulting in mutations, partly because they can infect various animals where dual infections can occur, giving rise to new hybrid strains. The infections occur in epidemics, which may occur every 2–3 years and which vary in size and severity; perhaps the most important of the three types of i. (A, B, and C).

Asian i., a worldwide i., apparently originating in China in the summer of 1957, which produces a milder disease than that of the pandemic of 1917–1919.

i. B, i. caused by strains of influenza virus type B; outbreaks are usually more limited than those due to influenza virus type A, although infections by the two types are clinically indistinguishable; occasionally associated with Reye syndrome.

i. C, i. caused by strains of type C influenza virus; the disease is milder than that caused by types A and B and has become uncommon in recent years.

endemic i., i., usually of a less severe type, occurring with some degree of regularity during the winter season, especially in the larger cities of the world. SYN i. nostras.

Hong Kong i., influenza caused by a serotype of influenza virus type A and first identified in Hong Kong in 1968.

i. nos'tras, SYN endemic i.

Russian i., a pandemic of a strain i. A virus thought to have originated in Russia; occurred in 1978.

Spanish i., i. that caused several waves of pandemic in 1918–1919, resulting in more than 20 million deaths worldwide; it was particularly severe in Spain (hence the name), but now is thought to have originated in the U.S. as a form of swine i.

swine i., an acute respiratory disease of swine caused by strains of influenza virus type A; it is believed to have become adapted to swine in the United States during the great human pandemic in 1918; fatal cases, as in such cases of pandemic i. in humans, are commonly associated with secondary bacterial pneumonia.

in·flu·en·zal (in-floo-en'zăl). Relating to, marked by, or resulting from influenza.

In·flu·en·za vi·rus (in-floo-en'ză-vī-rŭs). The family of Orthomyxoviridae contains 3 genera: Influenzavirus A, B; Influenzavirus C; and "Thogoto-like viruses." Each type of virus has a stable nucleoprotein group antigen common to all strains of the type, b distinct from that of the other type; the genome is negative sen single-stranded RNA in 6–8 segments; each also has a mosaic surface antigens (hemagglutinin and neuraminidase) that chara terize the strains and that are subject to variations of two kinds: a rather continual drift that occurs independently within the h magglutinin and neuraminidase antigens; 2) after a period years, a sudden shift (notably in type A virus of human origin) a different hemagglutinin or neuraminidase antigen. The sudde major shifts are the basis of subdivisions of type A virus human origin, which occur following infection of the animal ho with 2 different strains at the same time, resulting in a hybri virus. Strain notations indicate type, geographic origin, year isolation, and, in the case of type A strains, the characterizin subtypes of hemagglutinin and neuraminidase antigens (e.g. A/Hong Kong/1/68 (H_3 N_2); B/Hong Kong/5/72).

in·fold (in-fōld'). To inclose within a fold, as in "infolding" a ulcer of the stomach, in which the walls on either side of th lesion are brought together and sutured.

informatics (in-for-mat'iks). **1.** The study of information an ways to process and handle it, especially by means of informatio technology, i.e., computers and other electronic devices for rapi transfer, processing, and analysis of large amounts of data. **2.** The science of arranging and organizing the product of genomic and functional genomic studies so that useful insight can result. SE ALSO bioinformatics. [*informa*tion + -ics]

in·formed con·sent. Voluntary consent given by a person or a responsible proxy (e.g., a parent) for participation in a study, immunization program, treatment regimen, invasive procedure, etc., after being informed of the purpose, methods, procedures, benefits, and risks. The essential criteria of i. c. are that the subject has both knowledge and comprehension, that consent is freely given without duress or undue influence, and that the right of withdrawal at any time is clearly communicated to the subject. Other aspects of i. c. in the context of epidemiologic and biomedical research, and criteria to be met in obtaining it, are specified in *International Guidelines for Ethical Review of Epidemiologic Studies* (Geneva: CIOMS/WHO 1991) and *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (Geneva: CIOMS/WHO 1993).

in·for·mo·fers (in-fōr'mō-fers). Name suggested for the protein particles that appear when RNA is removed from nucleoprotein particles. [information + -fer]

in·for·mo·somes (in-fōr'mō-sōmz). Name suggested for the bodies composed of messenger (informational) RNA and protein that are found in the cytoplasm of animal cells. [*informa*tion + G. *sōma*, body]

infra-. A position below the part denoted by the word to which it is joined. [L. below]

in·fra·ax·il·lary (in'fră-ak'si-lār-ē). SYN subaxillary.

in·fra·bulge (in'fră-bŭlj). **1.** That portion of the crown of a tooth gingival to the height of contour. **2.** That area of a tooth where the retentive portion of a clasp of a removable partial denture is placed.

in·fra·car·di·ac (in'fră-kar'dē-ak). Beneath the heart; below the level of the heart.

in·fra·ce·re·bral (in'fră-ser'e-brăl). Pertaining to that portion of the nervous system below the level of the cerebrum.

in·fra·cla·vic·u·lar (in'fră-kla-vik'ū-lăr). SYN subclavian (1).

in·fra·clu·sion (in-fră-kloo'zhŭn). The state wherein a tooth has failed to erupt to the maxillomandibular plane of interdigitation. SYN infraocclusion, infraversion (3).

in·fra·cor·ti·cal (in-fră-kōr'ti-kăl). Beneath the cortex of an organ, mainly the brain or kidney. SEE subcortical.

in·fra·cos·tal (in-fră-kos'tăl). SYN subcostal (1).

in·fra·cot·y·loid (in-fră-kot'i-loyd). Below the acetabulum or cotyloid cavity.

in·fra·cris·tal (in-fră-kris'tăl). Below the supraventricular crest of the right ventricle; usually used in reference to ventricular septal defect. [infra- + L. *crista*, crest]

in·frac·tion (in-frak'shŭn). Obsolete term for fracture; especially

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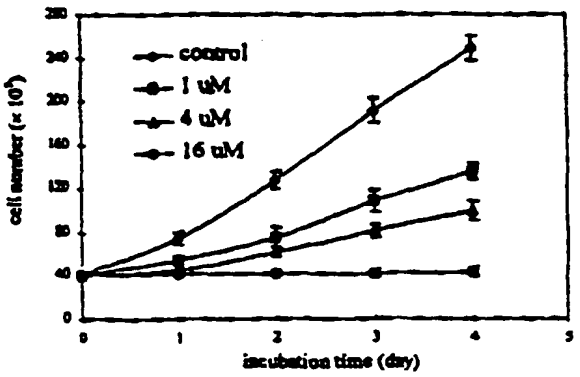
(54) Title: COMPOSITIONS OF BOSWELLIC ACIDS DERIVED FROM BOSWELLIA SERRATA GUM RESIN, FOR TREATING LYMPHOPROLIFERATIVE AND AUTOIMMUNE CONDITIONS

(57) Abstract

Method of treatment of lymphoproliferative and autoimmune disorders with a new composition of four boswellic acids including β–boswellic acid, 3–O–acetyl–β–boswellic acid, 11–keto–β–boswellic acid, and 3–O–acetyl–11–keto–β–boswellic acid. Boswellic acids of invention have been obtained in a novel industrial process from the gum resin of Boswellia serrata tree, providing standardized composition which inhibits DNA, RNA and protein synthesis of the target cell without cytotoxic effects. Composition of invention provides advantage of irreversible cytostatic therapy, equivalent to biological effects of a cytotoxic therapy without killing body cells.



Inhibitory effect of compound 4 on the growth of HL-60 cells. Results represent the average values for three experiments each performed in triplicate. Significantly different from control, $P < 0.05$.

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COMPOSITIONS OF BOSWELLIC ACIDS DERIVED FROM BOSWELLIA SERRATA GUM RESIN, FOR TREATING LYMPHOPROLIFERATIVE AND AUTOIMMUNE CONDITIONS

Background of the Invention

The present invention concerns new compositions of boswellic acids, methods of using the compositions or individual boswellic acids to treat lymphoproliferative and autoimmune conditions, and two new methods of isolating the new compositions.

Boswellia serrata (N.O. Burseraceae) is a large, branching, deciduous tree which grows abundantly in the dry, hilly parts of India. It is known as "Dhup", Indian Frankincense or Indian Olibanum. The gum resin exudate of *Boswellia serrata*, known in the vernacular as "Salai guggal", has been used in the Ayurvedic system of medicine for the management of rheumatism, respiratory diseases, and liver disorders. The major use of *Boswellia serrata* in contemporary medicine is as an anti-arthritic and anti-inflammatory pharmacological agent.

The active principles of the gum resin, boswellic acids, emerge as leading non-steroidal, anti-inflammatory compounds (drugs) NSAID with broad biological activities and low ulcerogenic index. Preclinical studies established that an alcoholic extract of the gum resin displayed marked anti-inflammatory activity in mice and rats, and also inhibited the formation of leukotrienes in rat peritoneal neutrophils *in vitro*. Boswellic acids decreased the formation of inflammatory leukotriene B4 (B4 is an outcome of the arachidonic acid metabolism) in rat peritoneal neutrophils in a dose-dependent way with IC50 values ranging from 1.5 to 7uM. The anti-inflammatory mechanism of action of boswellic acids inhibited the leukotriene synthesis via 5-lopoxygenase, but did not affect the 12-lipoxygenase and cyclooxygenase activity. Additionally, boswellic acids did not impair the peroxidation of arachidonic acid by iron and ascorbate. These results suggest that boswellic acids are specific, non-redox inhibitors of leukotriene synthesis either interacting with 5-lipoxygenase or blocking its translocation.

Safayhi, H. et al (1992) established and prior art by Ammon et al (EP 0 552 657) teaches that six boswellic acids are involved in the inhibition of 5-lipoxygenase, thus potentially blocking synthesis of inflammatory leukotrienes and thus useful in treatment of clinical conditions like inflammatory bowel diseases, arthritis, asthma, psoriasis and chronic form of hepatitis. These six compounds listed by Ammon in order of their

biological strength based on IC50-values are as follows: 1. acetyl-11-keto-beta-boswellic acid. 2. Beta-boswellic acid. 3. 11-keto-beta-boswellic acid. 4. Alpha-boswellic acid. 5. Acetyl-beta-boswellic acid and 6. Acetyl-alpha-boswellic acid. Ammon et al (WO 97/07796) also teaches that boswellic acids can be also used as inhibitor of elevated leucocyte elastase or plasmin activity and useful in clinical conditions characterized by the elevated activity of the elastase and/or plasmin. The anti-inflammatory properties of the gum resin is attributed to the presence of "boswellic acids". Boswellic acids were found to inhibit two pro-inflammatory enzymes, 5-lipoxygenase (which generates inflammatory leukotrienes) and Human Leukocyte Elastase (HLE). HLE is a serine protease which initiates injury to the tissues. which in turn triggers the inflamation. Studies by Safayhi. H. et al (1997) showed that Acetyl-11-keto-β-boswellic acid decreased the activity of human leukocyte elastase (HLE) *in vitro* with an IC_{50} value of about 15 μM.

Prior art by Lee Yue-Wei et al (U.S. Patent No. 5,064,823) also teaches that pentacyclic triterpenoid compounds such as alpha boswellic acid and its acetate, beta boswellic acid and its acetate have an inhibitory effect on topoisomerase I and topoisomerase II which according to authors may result in increased cancer cell differentiation. That process may be considered a cancer treatment modality.

An alcoholic extract of the gum resin was examined for anti-carcinogenic properties by Mukherji S. et al (1970). When tested on mice with Ehrlich ascites carcinoma and S-180 tumor. the extract inhibited tumor growth and increased the life span of experimental animals with carcinoma.

Summary of the Invention

Despite recognized potential of boswellic acids as NSAIDs and as a promising cancer fighting compounds. there are two major obstacles which stand in way of utilization boswellic acids in the health care: (a) poorly understood relationships between structure/composition of boswellic acids and their biological utility, and (b) lack of the boswellic acids product standardized on the basis of clearly defined structure function claim.

In the present invention. four purified boswellic acids. individually or in mixtures. were discovered to be effective in treating lymphoproliferative conditions

and autoimmune diseases in animals, including humans. The four purified boswellic acids were shown, in the present invention, in studies to evaluate the effects against macromolecular biosynthesis and cellular growth of human leukemia HL-60 cells. The four major pentacyclic triterpenic (boswellic) acids present in the acidic extract of *Boswellia serrata* gum in the present invention are:

- β–Boswellic Acid (I)
- Acetyl-β–Boswellic Acid (II)
- 11-keto-β–Boswellic Acid (III)
- Acetyl-11-keto-β–Boswellic Acid (IV)

Figures 1, 2, and 3 show the inhibitory effects of compounds I-IV on the DNA, RNA and protein synthesis of HL-60 cells, respectively (in Fig. 1-3, lines 1, 2, 3 and 4 refer to the data of compounds I, II, III and IV, respectively). Tables 1 and 2 show the inhibitory effect of a "total organic acids" extract of the exudate of *Boswellia serrata* on DNA, RNA and protein synthesis or growth in HL-60 cells. Table 3 shows the inhibitory effect of the "total organic acids" extract of the exudate of *Boswellia serrata* on the incorporation of [^{3}H]thymidine into the DNA of HL-60 cells. The initial rates of incorporation of [^{3}H]-thymidine, [^{3}H]-uridine and [^{3}H]-leucine into trichloroacetic acid (TCA)-insoluble material were utilized to estimate the rates of DNA, RNA, and protein synthesis, respectively, in HL-60 cells. All of the inhibitory effects of compounds I-IV and the alcoholic extract on DNA, RNA and protein synthesis of HL-60 cells were in a dose-dependent manner. Compounds I, II, III and IV exhibited 50% inhibitory activity on the incorporation of [3H]-thymidine into DNA at concentrations of 3.7, 1.4, 0.9 and 0.6 μM, respectively, the incorporation of [3H]-uridine at concentrations of 7.1, 2.3, 2.2 and 0.5 μM, respectively, and the incorporation of [3H]-leucine into protein at concentrations of 6.3, 5.4, 5.1 and 4.1 μM, respectively, in cultured HL-60 cells incubated for 2 hours.

Comparison of the IC50 values indicated that the order of inhibitory activity for compounds I-IV is IV>III>II>I. This observation is a principle behind the new composition of boswellic acids effective in lymphoproliferative and autoimmune disorders. The discovered relationship between structure and activity of specific boswellic acids in inhibition of DNA, RNA and protein synthesis has not been

previously reported. Our research has determined for the first time that (1) 11-keto group of boswellic acids is a principal moiety for the above described biological activity, and (2) 3-0-acetyl group amplifies that activity further resulting in a predictable cytostatic and immunomodulatory effects of boswellic acids.

It has been further determined that compound IV, which induced the most pronounced inhibitory effects on DNA, RNA and protein synthesis in HL-60 cells, had an irreversible inhibitory action on DNA synthesis. In this experiment HL-60 cells were preincubated with compound IV at 2 and 8 μM for 30 min at 37°C, washed with phosphate buffer saline and [3H]-thymidine was added to the culture. At desired times, the reactions were terminated and the rates of DNA synthesis were determined. The results (Fig. 4) showed that the inhibitory effect on DNA synthesis was still dependent upon the concentrations of compound IV and identical to that without washing. This finding suggested that the inhibitory action of compound IV on DNA synthesis was irreversible.

The effect of compound IV on cellular growth of HL-60 cells was tested. As shown in Fig. 8, compound IV depressed the growth of HL-60 cells in a dose-dependent manner. Addition of compound IV at 1, 4, or 16 μM to HL-60 cells and incubation at 37°C for 4 days inhibited the cellular growth by 54.5, 71.8 or 98.6%. In order to test whether this growth was the result of cell cytotoxicity, the effects of this compound on cell viability were examined after 4 days incubation using the trypan blue exclusion method. The cells viability at concentrations of 0, 1, 4, 16 μM were 97.0, 96.8, 96.5, or 96.7%, respectively.

This experiment showed that compound IV at the concentrations which significantly inhibited cell growth, did not affect cell viability. These results indicated that inhibition of the cell growth is due to the cytostatic rather then cytotoxic effects. The inhibition of cell proliferation can be explained by its interference with biosynthesis of DNA, RNA and protein all of which are required for cell proliferation. These results for the first time establish that composition of boswellic acid enriched with the compound IV can be used as cytostatic and immunomodulatory preparation, due to its profound and well defined effect on myeloid cell metabolism.

Within the scope of the present invention are methods of preventing or treating lymphoproliferative disorders or autoimmune diseases by administering a composition comprising a "total organic acids" extract obtained from *Boswellia serrata*, administering compound I, II, III or IV individually or administering a mixture comprising two, three or all four of compounds I, II, III and IV in humans or animals in need of such a prevention or treatment. Also within the scope of the present invention are methods of preventing or treating tumors or inflammatory disorders by administering the composition comprising the "total organic acids" extract obtained from *Boswellia serrata* or administering compound I, II, III or IV individually or administering a mixture comprising two, three or all four of compounds I, II, III and IV in humans or animals in need of such a prevention or treatment. The present invention also includes the composition comprising the "total organic acids" extract obtained from *Boswellia serrata*, a composition comprising two, three or four of compounds I-IV and two processes of obtaining boswellic acids or of obtaining the composition comprising the "total organic acids" extract obtained from *Boswellia serrata*.

The lymphoproliferative disorders that can be treated with the methods of using boswellic acids of the present invention include leukemia and lymphoma. Leukemia that can be treated by the methods of the present invention include myeloid leukemia, acute myelogenous leukemia, acute lymphocytic leukemia, acute non-lymphocytic leukemia, chronic lymphocytic leukemia, and hairy cell leukemia. The autoimmune diseases that can be treated with the methods of using boswellic acids of the present invention include, for example, psoriasis, sarcoidosis, systemic lupus erythematosis, Graves' disease, Hashimoto's thyroiditis, silent thyroiditis, Crohn's disease, Goodpasture syndrome, insulin-dependent diabetes mellitus, insulin-resistant diabetes mellitus, myasthenia gravis, Addison's disease, idiopathyic hypoparathyroidism, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, rheumatoid arthritis, and scleroderma. The methods of using boswellic acids of the present invention are also effective in treating tumors, including, for example, breast tumors, ovarian tumors, uterine tumor, lung tumors, liver tumors,

renal tumors. prostatic tumors. pancreatic tumors. tumors of the gastrointestinal tract. e.g. colorectal tumors. brain tumors. and head and neck tumors.

The following tables present data concerning the biological effects of an alcoholic extract of the exudate of *Bosweilia serrata*. Table 1 below presents data on the effects of the alcoholic extract of the exudate of *Boswellia serrata* on the DNA synthesis. RNA synthesis and protein synthesis in HL-60 cells in culture.

Table 1

BSE added	DNA synthesis		RNA syntheses		Protein synthesis	
(μm)	% Control	% Inhibition	% Control	% Inhibition	% Control	% Inhibition
0	100	0	100	0	100	0
0.75	80	20	91	9	70	30
1.5	45	55	64	36	52	48
3.0	35	65	62	38	26	74
6.0	23	77	20	80	12	88
12.0	19	81	10	90	9	91
25.0	18	82	8	92	8	92

Various concentrations of the *Bosweilia serrata* extract. as indicated above. were added to 1 mL of HL-60 cells suspended in RPMI medium. [^{3}H]thymidine (50 μCi/μmol: 3 mL), [^{3}H]uridine (55 μCi/μmol: 5 μL), [^{3}H]leucine (200 μCi/μmol: 10 μL), were added to the cell suspension and incubated at 37°C for 120 min. Reactions were terminated by addition of 3 mL of cold PBS. and the rates of DNA. RNA. and protein synthesis were determined.

Table 2 below presents data on the effect of the alcoholic extract of the exudate of *Bosweilia serrata* on the growth of HL-60 cells in culture. The alcoholic extract of the exudate of *Bosweilia serrata* inhibited the growth of HL-60 cells in a concentration dependent fashio.

Table 2

Incubation time (hours)	Concentration of BSE (μM)			
	0	4	12	50
0	25 ± 2.3	25 ± 2.3	25 ± 2.3	25 ± 2.3
24	45 ± 2.1	40 ± 4.2 (25%)	39 ± 3.7 (30%)	30 ± 4.0 (75%)
48	71 ± 1.5	66 ± 4.7 (11%)	57 ± 3.5 (30%)	27 ± 2.0 (97%)
72	102 ± 2.1	95 ± 2.9 (9%)	72 ± 7.8 (40%)	25 ± 1.2 (100%)
96	166 ± 16.6	159 ± 11 (5%)	102 ± 2.6 (45%)	31 ± 2.2 (96%)

Various concentrations of BSE, as indicated above, were added to the HL-60 cell cultures. These cultures were counted daily using a hemacytometer under a microscope with 10x magnification every 24 hours. Data are expressed as the mean = SE calculated from triplicate studies. Data in parentheses are the percent inhibition of cell growth.

Other than the inhibitory effects on the synthesis of RNA and protein in HL-60 cells grown in culture, the present invention demonstrated that boswellic acids have an inhibitory effect on DNA synthesis in HL-60 cells. Table 3 below shows that the alcoholic extract of the exudate of *Boswellia serrata* can inhibit DNA synthesis in HL-60 cells as demonstrated by an inhibition of the incorporation of ^{3}H-labeled thymidine into the DNA of HL-60 cells. Similar to the results in Table 2, Table 3 demonstrates that the inhibitory effect of the alcoholic extract of the exudate of *Boswellia serrata* on DNA synthesis in HL-60 cells exhibited a concentration dependent response.

Table 3

Incubation time	Concentration of BSE (μM)			
(min)	0	4	12	50
		(cpm/5 x 10^5 cells)		
0	279 ± 76	352 ± 114	312 ± 54	225 ± 15
120	11112 ± 1897	4039 ± 737 (69%)	2794 ± 306 (77%)	1893 ± 505 (86%)

[^{3}H]Thymidine (3 μL; 50 μCi/μmol), vehicle or various concentrations of BSE in vehicle were added to 1 mL of HL-60 cells (5 x 10^5 cells/mL) in culture, and the cultures were incubated at 37°C for 120 min. Data are expressed as the mean ± SE calculated from triplicate studies. Data in parentheses are the percent inhibition of [^{3}H]thymidine incorporation into the DNA of HL-60 cells.

Brief Description of the Drawings

Fig. 1 depicts the effects of compounds I-IV on the DNA synthesis in HL-60 cells.

Fig. 2 depicts the effects of compounds I-IV on the RNA synthesis in HL-60 cells.

Fig. 3 depicts the effects of compounds I-IV on the protein synthesis in HL-60 cells.

Fig. 4 shows the inhibitory effects of compound IV on the DNA synthesis in HL-60 cells.

Fig. 5, 6 and 7 show the β-boswellic acids contents in 6 commercial samples of *Boswellia serrata* extract.

Fig. 8 shows the inhibitory effect of compound IV on the growth of HL-60 cells.

Detailed Description of the Invention

Based on our experimental data on relationship between structure and function of the four boswellic acids of invention, a novel manufacturing and standardization process for boswellic acids have been developed. The new

standardization process resulted in changes in the nomenclature of the boswellic acids preparation. The new nomenclature included the following changes.

The phrase "total organic acids" from *Boswellia serrata* refers to an organic acid fraction of an extract of *Boswellia serrata* or *Boswellia serrata* gum. The "total organic acids" from *Boswellia serrata* constitute approximately 65-70%, by weight, of the total alcoholic extract of *Boswellia serrata*. In the methods of treatment of the present invention, the daily effective dose, for a 70 kg subject to be treated, is 1-5000 mg "total organic acids" from *Boswellia serrata*, 2 to 4 times a day. The preferred daily effective dose is 10-500 mg "total organic acids", 2 to 4 times a day. The more preferred daily effective dose is 100-400 mg "total organic acids", 2 to 4 times a day. The most preferred daily effective dose is 200 mg "total organic acids", 3 times a day. For humans or animals of a body weight other than 70 kg, the above doses can be adjusted accordingly based on the body weight or the body surface area based on methods known in the art.

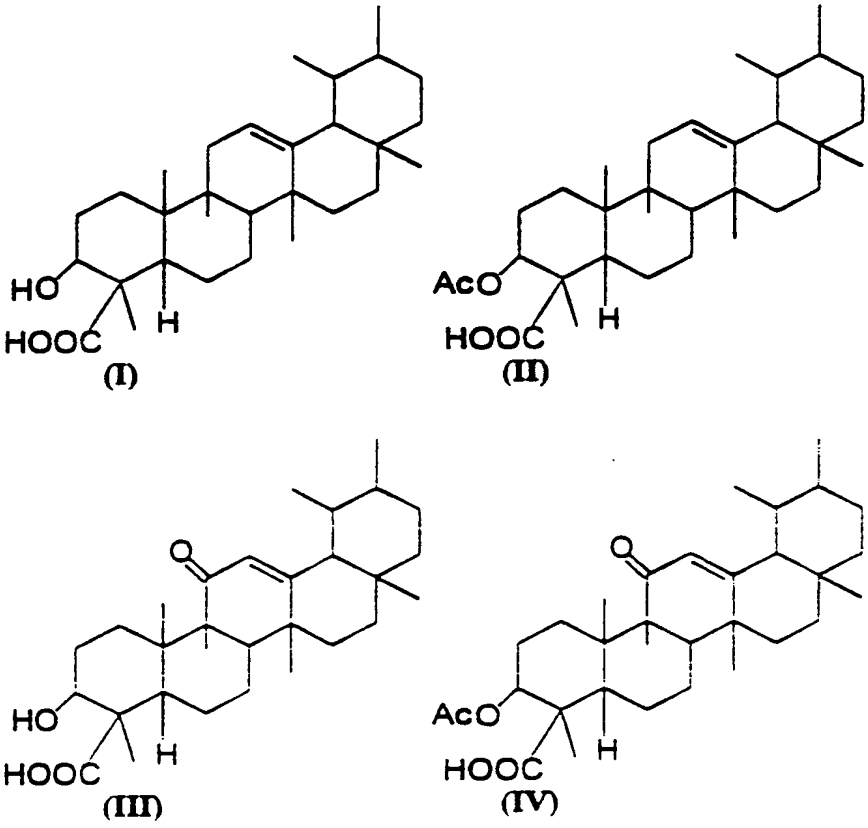
The term "pure boswellic acids" indicates the four major boswellic acids in each dosage form. The "pure boswellic acids" can contain two, three or all four of the four major boswellic acids, i.e. β-boswellic acid (I), acetyl-β-boswellic acid (II), 11-keto-β-boswellic acid (III), and acetyl-11-keto-β-boswellic acid (IV). The "pure boswellic acids" constitute approximately 25% of the "total organic acids". In the methods of treatment of the present invention, the daily effective dose, for a 70 kg subject to be treated, is 0.25-1250 mg "pure boswellic acids", 2 to 4 times a day. The preferred daily effective dose is 2.5-125 mg "pure boswellic acids", 2 to 4 times a day. The more preferred daily effective dose is 25-100 mg "pure boswellic acids", 2 to 4 times a day. The most preferred daily effective dose is 50 mg "pure boswellic acids", 3 times a day. For humans or animals of a body weight other than 70 kg, the above doses can be adjusted accordingly based on the body weight or the body surface area based on methods known in the art.

The total organic acids extract from *Boswellia serrata* can be administered by topical, inhalational, parenteral or oral routes, or by nasal spray or suppositories. Similarly, pure boswellic acids, individual boswellic acids, or mixtures thereof, can

be administered by topical, inhalational, parenteral or oral routes, or by nasal spray or suppositories.

Although there are other components in the Boswellii serrata gum (e.g. alpha and gamma-Boswellic acids), the four major pentacyclic triterpenic (boswellic) acids present in the acidic extract of *Bosweilia serrata* gum of the invention used for standardization are:

- β–Boswellic Acid (I)
- Acetyl-β–Boswellic Acid (II)
- 11-keto-β–Boswellic Acid (III)
- Acetyl-11-keto-β–Boswellic Acid (IV)



Commercial samples of *Boswellia serrata* extracts vary greatly in their contents of boswellic acids, which limits, as previously mentioned, a reliable use of boswellic acids in medical and veterinary applications. The analytical results for six commercial samples are indicated in Figure 5, Figure 6 and Figure 7, in terms of content of boswellic acids, their composition, and total organic acids content respectively. In many commercial samples, the most active β-Boswellic acids are available in negligible quantities only. The total organic acids content in these samples as determined by titration is indicated in Figure 7.

The above analytical results make it evident that (a) there is need for accurately standardized boswellic acid product by the HPLC method, and (b) that the active components in *Boswellia serrata* extract cannot be accurately predicted based on titrimetric method analysis. It is equally interesting to note that while the titrimetric method gives more than 50% by weight of organic acids, several of the commercially available products contain only negligible amounts of the two key boswellic acids, namely 11- keto- beta- and acetyl- 11- keto- beta- boswellic acids (Figure 6).

Method of extraction of boswellic acids

By applying a prior art extraction method on a typical sample of *Boswellia serrata*, a composition was obtained containing the four boswellic acids, compounds I-IV, at concentrations shown below:

Component	**% by weight**
I. β–Boswellic Acid	10.1
II. Acetyl-β–Boswellic Acid	6.8
III. 11-keto-β–Boswellic Acid	5.1
IV. Acetyl-11-keto-β–Boswellic Acid	3.8
Total	**25.8**

The "total organic acids" value of this preparation by titration method was: 70.9% by weight.

The present invention includes a first new process of extraction to obtain boswellic acids to ascertain a minimum yield of total boswellic acids by HPLC of minimum 38 weight%, with compound IV of not less than 4 weight%, compound III

of not less than 5 weight%. compound II of not less than 10 weight% and compound I of not less than 14 weight%. The yield of boswellic acids obtainable by the first new process of the present invention is much higher than the prior art process of extraction. Flow chart of old process versus the first new extraction and manufacturing process is shown below.

PROCESS COMPARISON

OLD PROCESS	NEW PROCESS
1. *Boswellia serrata*	1. *Boswellia serrata*
2. Extract with hot isopropyl alcohol	2. Extract with hot C_1-C_6 alcohol, e.g. isopropyl alcohol, butanol
3. Concentrate the isopropyl alcohol extract to 50%	3. Strip off the alcohol extract completely
4. Treat with KOH to pH 9.5 at 60°C	4. Treat with an alkaline substance, e.g. alkali such as KOH or NaOH, to pH>9.5 at room temperature
5. Remove isopropyl alcohol and wash with ether	5. Wash with an organic solvent, such as an ester or ketone solvent
6. Treat aqueous layer with hydrochloric acid to pH 4	6. Treat aqueous layer with hydrochloric acid to pH 4
7. Obtain precipitate	7. Obtain precipitate
8. Wash precipitate with water	8. Wash precipitate with water
9. Dry the precipitate	9. Dry the precipitate at <50°C

In the first new process of extraction to obtain boswellic acids. an example of the organic solvent used in step 5 is ethyl acetate. As needed. modifications. obvious to one skilled in the art. of the new process of extraction to obtain boswellic acids can be done. The modified new process of extraction is also within the scope of the present invention.

Example of manufacturing process of boswellic acid of invention

Process Data Sheet For The Manufacture Of Boswellin 100 kg

1. Charge the extractor with Boswellia serrata gum 555 kg.
2. Charge isopropyl alcohol to the soaking level (1100L–false bottom capacity).

3. Pass steam into the jacket and maintain the temperature at 68-70 deg. C in the core body of the reactor.
4. Drain the extract into a reactor and concentrate at 70 deg. C to strip off isopropyl alcohol completely.
5. Charge isopropyl alcohol to the soaking level 550 L and repeat the step 3 to 4
6. Repeat step 5
7. Charge 560 L of 5 weight% aqueous KOH. then stir at room temperature for 3 hours.
8. Wash with ethyl acetate 830 L.
9. Drain the ethyl acetate layer and collect aqueous layer.
10. Repeat step 8 and 9 two times with 550 L ethylacetate and collect the aqueous layer.
11. Charge the aqueous layer (from steps 9 and 10) into a reactor.
12. Add slowly 6 N HCl to pH 3-4 (~30L) while stirring at room temperature.
13. Forms a precipitate.
14. Add 1000L of water and let it stand at room temperature for 8 hours (or less depending on the observation).
15. Collect the precipitate (by draining into a nutsch and scooping), wash with water.
16. Check for Boswellin in aqueous portion. if absent discard.
17. Dry the prcipitate not above 50 deg. C.
18. Yield expected ~ 100 kg (assay by HPLC 38-40%).

<u>Assay by HPLC for Beta Boswellic acids</u>

Mobile phase:

Mobile phase A: 1000 ml of Acetonitrile with 0.05ml (1 drop) of glacial acetic acid. filter and degas.

Mobile phase B: Mix water and acetonitrile in the ratio150:850 with 0.05ml(1 drop) of glacial acetic acid filter and degas.

Use gradient program

Time	A concentration	B concentration
0 min	90%	10%

15 min	20%	80%
20 min	0%	100 %
25 min	50%	50%
30min	100%	0%
30min	stop	

Sample preparation:

Weigh accurately about 200 mg of the sample and transfer into a 50ml volumetric flask. Add 25 ml of methanol to dissolve the sample. and sonicate for 3 minutes, dilute to volume. mix.

Standard preparation:

1. Beta-boswellic acid: weigh accurately about 25 mg of the standard and transfer into a 10 ml volumetric flask. Add 5 ml of methanol to dissolve the sample, sonicate for 3 minutes. dilute to volume, mix.
2. Acetyl-beta-boswellic acid: weigh accurately about 500 mg of standard and transfer into a 10 ml volumetric flask. Add 5 ml of methanol to dissolve the sample, sonicate for 3 minutes, dilute to volume, mix.
3. 11-Keto-beta-boswellic acid; weigh accurately about 25 mg of the standard and transfer into a 25 ml volumeric flask. Add 15 ml of methanol to dissolve the sample. sonicate for 3 minutes, dilute to volume, mix.
4. Acetyl-11-keto-beta-boswellic acid: weigh accurately about 25 mg of the standard and transfer into a 25 ml volumetric flask. Add 15 ml of methanol to dissolve the sample, sonicate for 3 minutes. dilute to volume. mix.

Alternatively, weigh accurately about 25 mg of the standard (which contains known concentration of beta-boswellic acid) into 25 ml volumetric flask. Add 15 ml of methanol to dissolve the sample. sonicate for 3 minutes. dilute to volume. mix.

Chromatographic system:

The liquid chromatograph is equipped with 210nm and 256 nm UV detector and a 250 x 4.6 mm column that contains the packing C18 or ODS (Sigma/Aldrich column is used). The flow rate is 1.0 ml per min. The relative standard deviation for replicate injection of Standard preparation should not be more than 2%.

Procedure:

Separately inject equal volume (20ul) of the standard preparations and sample preparation into the chromatograph, record the responses for the peak of beta-boswellic acid and acetyl-beta-boswellic acid at 210nm and for the peaks of 11-keto-beta-boswellic acid and acetyl-11-ketoboswellic acid at 245 nm and calculate the percentage by weight of each boswellic acids as follows:

The following are the retention times of the four beta Boswellic acids:

1. Beta-boswellic acid.....17.4min
2. 3-acetyl beta-boswellic acid.....26.0min
3. 11-keto-beta-boswellic acid.....7.2min
4. 3-acetyl-11-keto-beta-boswellic acid.....10.4min

$$\frac{\text{Area of Sample} \times \text{Standard concentration in mg/ml} \times \text{Purity of the standard}}{\text{Area of Standard} \times \text{Sample concentration in mg/ml}}$$

Results of HPLC assay of pentacyclic triterpinic acids

Description	Old Plant Batch	RD/BS/21 New R&D Batch (1 kg)	New Trial Plant Batch (100 kg)
Beta-Boswellic acid	10.3 wt%	15 wt%	14 wt%
Acetyl-beta-boswellic acid	7.1 wt%	11 wt%	13.5 wt%
11-keto-boswellic acid	3.3 wt%	6.5 wt%	6.5 wt%
Acetyl-keto-beta-boswellic acid	3.4 wt%	7.6 wt%	7.5 wt%
TOTAL%	24.1 wt%	40.1 wt%	41.5 wt%

Wherein "Old" means the old process and "New" means the new process.

The "total organic acids" extract of the present invention can be obtained by a process comprising the following steps:

(1) providing a *Boswellia serrata* component:

(2) extracting the component with a C_1-C_6 alcohol, e.g. isopropyl alcohol, to obtain an alcohol extract:

(3) remove the C_1-C_6 alcohol from the alcohol extract to obtain a liquid:

(4) treat the liquid with an alkaline substance, such as an alkali, e.g. KOH, to obtain an alkaline liquid:

(5) wash the alkaline liquid with an organic solvent, e.g. ethyl acetate;

(6) remove the organic solvent to obtain an aqueous liquid; and thereafter

(7) treat the aqueous liquid with an acid, e.g. hydrochloric acid, to form the "total organic acids" extract as a precipitate.

Preferably, the *Boswellia serrata* component used is *Boswellia serrata* gum. The component in step (2) is preferably treated with hot isopropyl alcohol at a temperature of about 50-80°C, about 60-75°C, about 68-72°C or about 70°C. The treatment with KOH in step (4) preferably is carried out at pH>9.5. Step (7) is preferably conducted by treating the aqueous liquid with hydrochloric acid at about pH 3 to 4 to obtain a precipitate, which optionally can be washed with water and dried at a temperature less than about 50°C.

From the "total organic acids" extract obtained by the new process of the present invention, individual pure oswellic acids, i.e. compounds I, II, III or IV, can be obtained by chromatographic methods known in the prior art. The pure compound I, II, III and IV can also be obtained by synthetic processes known in the art. The individual pure oswellic acid can be mixed in any ratio to obtain desired mixtures.

The present invention includes compositions comprising the "total organic acids" extract obtained by the new process of the invention, any one of pure compound I, II, III or IV, or mixtures of two, three or all of compounds I-IV, mixed with a physiologically acceptable carrier or excipient.

The compositions of the present invention can comprise compound I : compound II : compound III : compound IV in any proportions. Preferably, the compositions comprise compound I : compound II : compound III : compound IV of 10-20 : 5-25 : 1-15 : 1-20 (or 15-20 : 5-25 : 1-15 : 1-20). More preferably, the compositions comprise compound I : compound II : compound III : compound IV of 12-17 : 7-18 : 3-10 : 2-15. Much preferred compositions of the present invention comprise compound I : compound II : compound III : compound IV of 14-16 : 8-17 : 4-9 : 3-10. Most preferred compositions of the present invention comprise compound I : compound II : compound III : compound IV of 15 : 10-15 : 5-8 : 4-8.

Another aspect of the present invention is a composition consisting essentially of, based on the total weight of the composition, β-boswellic acid of at least 12% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 1% by weight and acetyl-11-keto-β-boswellic acid of at least 1% by weight. This composition can contain other boswellic acids, e.g. 3a-hydroxy-urs-9,12-diene-24-oic acid or 2a,3a-dihydroxy-urs-12-ene-24-oic acid, each of which at a content of less than 1% by weight, based on the total weight of the composition. Preferably, the composition consists essentially of, based on the total weight of the composition, β-boswellic acid of at least 14% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 5% by weight and acetyl-11-keto-β-boswellic acid of at least 5% by weight. Also preferably, the composition consists essentially of, based on the total weight of the composition, β-boswellic acid of 12 to 35% by weight, acetyl-β-boswellic acid of 5 to 35% by weight, 11-keto-β-boswellic acid of 5 to 45% by weight and acetyl-11-keto-β-boswellic acid of 5 to 45% by weight. The composition, also preferably, consists essentially of, based on the total weight of the composition, β-boswellic acid of 12 to 30% by weight, acetyl-β-boswellic acid of 10 to 25% by weight, 11-keto-β-boswellic acid of 5 to 35% by weight and acetyl-11-keto-β-boswellic acid of 5 to 35% by weight. More preferably, the composition consists essentially of, based on the total weight of the composition, β-boswellic acid of 14 to 30% by weight, acetyl-β-boswellic acid of 10 to 20% by weight, 11-keto-β-boswellic acid of 5 to 25% by weight and acetyl-11-keto-β-boswellic acid of 5 to 25% by weight. Also more preferably, the composition consists essentially of, based on the total weight of the composition, β-boswellic acid of 14 to 35% by weight, acetyl-β-boswellic acid of 10 to 20% by weight, 11-keto-β-boswellic acid of 5 to 25% by weight and acetyl-11-keto-β-boswellic acid of 5 to 20% by weight. Also more preferably, the composition consists essentially of, based on the total weight of the composition, β-boswellic acid of 14 to 35% by weight, acetyl-β-boswellic acid of 10 to 20% by weight, 11-keto-β-boswellic acid of 5 to 20% by weight and acetyl-11-keto-β-boswellic acid of 5 to 25% by weight.

Another aspect of the present invention is a composition comprising three boswellic acids selected from the group consisting of β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid, wherein, based on the total weight of the composition, the amount of β-boswellic acid is at least 5% by weight, the amount of acetyl-β-boswellic acid of is least 5% by weight, the amount of 11-keto-β-boswellic acid is at least 5% by weight, and the amount of acetyl-11-keto-β-boswellic acid is at least 5% by weight. Preferably, in the composition, the amount of β-boswellic acid is 14 to 65% by weight, the amount of acetyl-β-boswellic acid is 5 to 65% by weight, the amount of 11-keto-β-boswellic acid is 5 to 60% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 5 to 60% by weight. Also preferably, in the composition, the amount of β-boswellic acid is 14 to 55% by weight, the amount of acetyl-β-boswellic acid is 10 to 55% by weight, the amount of 11-keto-β-boswellic acid is 5 to 50% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 5 to 50% by weight. Also preferably, in the composition, the amount of β-boswellic acid is 14 to 35% by weight, the amount of acetyl-β-boswellic acid is 10 to 35% by weight, the amount of 11-keto-β-boswellic acid is 5 to 40% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 5 to 40% by weight. Also preferably, in the composition, the β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid are derived from any natural source. Also preferably, in the composition, two of the three boswellic acids are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

Another aspect of the present invention is a composition comprising two boswellic acids selected from the group consisting of β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid, wherein, based on the total weight of the composition, the amount of β-boswellic acid is at least 5% by weight, the amount of acetyl-β-boswellic acid is least 5% by weight, the amount of 11-keto-β-boswellic acid is at least 5% by weight, and the amount of acetyl-11-keto-β-boswellic acid is at least 5% by weight. Preferably, in the composition, the amount of β-boswellic acid is 5 to 95% by weight, the amount of acetyl-β-boswellic acid is 5 to 95% by weight, the amount of 11-keto-β-boswellic

acid is 5 to 95% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 5 to 95% by weight. Preferably, in the composition, the amount of β-boswellic acid is 30 to 70% by weight, the amount of acetyl-β-boswellic acid is 30 to 70% by weight, the amount of 11-keto-β-boswellic acid is 30 to 70% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 30 to 70% by weight. Also preferably, in the composition, the amount of β-boswellic acid is 40 to 60% by weight, the amount of acetyl-β-boswellic acid is 40 to 60% by weight, the amount of 11-keto-β-boswellic acid is 40 to 60% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 40 to 60% by weight. Also preferably, in the composition, the two boswellic acids are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

Within the scope of the present invention is a composition comprising boswellic acids, wherein the boswellic acids consist of three substances selected from the group consisting of β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid, wherein, based on the total weight of the composition, the amount of β-boswellic acid is at least 5% by weight, the amount of acetyl-β-boswellic acid is least 5% by weight, the amount of 11-keto-β-boswellic acid is at least 5% by weight, and the amount of acetyl-11-keto-β-boswellic acid is at least 5% by weight. Preferably, in the composition, the amount of β-boswellic acid is 5 to 65% by weight, the amount of acetyl-β-boswellic acid is 5 to 65% by weight, the amount of 11-keto-β-boswellic acid is 5 to 65% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 5 to 65% by weight. Also preferably, in the composition, the amount of β-boswellic acid is 15 to 55% by weight, the amount of acetyl-β-boswellic acid is 15 to 55% by weight, the amount of 11-keto-β-boswellic acid is 15 to 55% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 15 to 55% by weight. Also preferably, in the composition, the amount of β-boswellic acid is 20 to 40% by weight, the amount of acetyl-β-boswellic acid is 20 to 40% by weight, the amount of 11-keto-β-boswellic acid is 20 to 40% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 20 to 40% by weight. Also preferably, in the composition, two of the three substances are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

Another aspect of the present invention is a composition comprising boswellic acids, wherein the boswellic acids consist of two substances selected from the group consisting of β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid, wherein, based on the total weight of the boswellic acids, the amount of β-boswellic acid is at least 5% by weight, the amount of acetyl-β-boswellic acid of is least 5% by weight, the amount of 11-keto-β-boswellic acid is at least 5% by weight, and the amount of acetyl-11-keto-β-boswellic acid is at least 5% by weight. Preferably, in the composition, the amount of β-boswellic acid is 10 to 90% by weight, the amount of acetyl-β-boswellic acid is 10 to 90% by weight, the amount of 11-keto-β-boswellic acid is 10 to 90% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 10 to 90% by weight. Also preferably, in the composition, the amount of β-boswellic acid is 20 to 80% by weight, the amount of acetyl-β-boswellic acid is 20 to 80% by weight, the amount of 11-keto-β-boswellic acid is 20 to 80% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 20 to 80% by weight. Also preferably, in the composition, the amount of β-boswellic acid is 30 to 70% by weight, the amount of acetyl-β-boswellic acid is 30 to 70% by weight, the amount of 11-keto-β-boswellic acid is 30 to 70% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 30 to 70% by weight. Also preferably, in the composition, the amount of β-boswellic acid is 40 to 60% by weight, the amount of acetyl-β-boswellic acid is 40 to 60% by weight, the amount of 11-keto-β-boswellic acid is 40 to 60% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 40 to 60% by weight. Also preferably, in the composition, the two substances are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

Another embodiment of the present invention is a method for inhibition of DNA, RNA and/or protein synthesis in a human or animal in need of the inhibition, wherein the method comprises a step of administering a DNA, RNA and/or protein synthesis inhibition effective amount of a composition to said human or animal, wherein the composition comprises β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid. Preferably, the composition comprises β-boswellic acid of at least 12% by weight, acetyl-β-

boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 1% by weight and acetyl-11-keto-β-boswellic acid of at least 1% by weight. More preferably, the composition comprises β-boswellic acid of 12 to 35% by weight, acetyl-β-boswellic acid of 5 to 35% by weight, 11-keto-β-boswellic acid of 5 to 45% by weight and acetyl-11-keto-β-boswellic acid of 5 to 45% by weight.

Another embodiment of the present invention is a method for irreversible inhibition of DNA synthesis in a human or animal in need of the inhibition, comprising a step of administering an irreversible DNA inhibition effective amount of a composition to said human or animal, wherein the composition comprises β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid. Preferably, for used in the method, the composition comprises β-boswellic acid of at least 12% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 1% by weight and acetyl-11-keto-β-boswellic acid of at least 1% by weight. For used in the method, the composition more preferably comprises β-boswellic acid of 12 to 35% by weight, acetyl-β-boswellic acid of 5 to 35% by weight, 11-keto-β-boswellic acid of 5 to 45% by weight and acetyl-11-keto-β-boswellic acid of 5 to 45% by weight.

Within the scope of the present invention is a method for the prevention or treatment of a lymphoproliferative disease in a human or animal in need of the prevention or treatment, wherein the method comprises a step of administering a lymphoproliferative disease prevention or treatment effective amount of a composition to said human or animal, wherein the composition comprises β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid. Preferably, for used in the method, the composition comprises β-boswellic acid of at least 12% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 1% by weight and acetyl-11-keto-β-boswellic acid of at least 1% by weight. More preferably, for used in the method, the composition comprises β-boswellic acid of 12 to 35% by weight, acetyl-β-boswellic acid of 5 to 35% by weight, 11-keto-β-boswellic acid of 5 to 45% by weight and acetyl-11-keto-β-boswellic acid of 5 to 45% by weight.

Another aspect of the present invention is a method for the prevention or treatment of an autoimmune disease in a human or animal in need of the prevention or treatment, wherein the method comprises a step of administering an autoimmune disease prevention or treatment effective amount of a composition to said human or animal, wherein the composition comprises β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid. Preferably, for used in the method, the composition comprises β-boswellic acid of at least 12% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 1% by weight and acetyl-11-keto-β-boswellic acid of at least 1% by weight. More preferably, for used in the method, the composition comprises β-boswellic acid of 12 to 35% by weight, acetyl-β-boswellic acid of 5 to 35% by weight, 11-keto-β-boswellic acid of 5 to 45% by weight and acetyl-11-keto-β-boswellic acid of 5 to 45% by weight.

Another aspect of the present invention is a method of inhibiting the synthesis of DNA, RNA and/or protein in a human or animal in need of the inhibition, comprising administering a DNA, RNA and/or protein synthesis inhibition effective amount of β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid or acetyl-11-keto-β-boswellic acid.

Another aspect of the present invention is a method for irreversibly inhibiting the synthesis of DNA in a human or animal in need of the inhibition, comprising administering a DNA synthesis reversible inhibition effective amount of β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid or acetyl-11-keto-β-boswellic acid.

Another aspect of the present invention is a method for preventing or treating a lymphoproliferative disease in a human or animal in need of the prevention or treatment, comprising administering a lymphoproliferative disease preventing or treating effective amount of β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid or acetyl-11-keto-β-boswellic acid.

Another aspect of the present invention is a method for preventing or treating an autoimmune disease in a human or animal in need of the prevention or treatment, comprising administering an autoimmune disease preventing or treating effective

amount of β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid or acetyl-11-keto-β-boswellic acid.

Also within the scope of the present invention are methods of using the compositions or boswellic acid(s), individually or mixtures thereof, of the present invention to make a medication for inhibiting the synthesis of DNA, RNA and/or protein, for irreversibly inhibiting the synthesis of DNA, for preventing or treating a lymphoproliferative or autoimmune disease.

Also preferably, in the compositions of the present invention, the β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid are derived from any natural source.

Within the scope of the present invention is a second new extraction process to obtain boswellic acids from *Boswellia serrata*. The second new extraction process of obtaining boswellic acids comprises the following steps:

(a) providing a *Boswellia serrata* component;

(b) extracting said *Boswellia serrata* component with carbon dioxide to obtain a fluid extract; and

(c) removing carbon dioxide from the fluid extract to obtain the boswellic acids.

In the second new extraction process, the *Boswellia serrata* component preferably is a gum or degummed resin from *Boswellia serrata*. The extracting step in the second new extraction process can be performed with subcritical extraction or supercritical extraction using liquid carbon dioxide. After the removal of carbon dioxide from the fluid extract, the so obtained boswellic acids can be, if necessary, subjected to further separation or purification, such as chromatography or selective precipitation in appropriate organic solvents.

Carbon dioxide may be used as an extracting solvent in either of two forms - subcritical and supercritical. Carbon dioxide has a critical temperature of 31.2°C and a critical pressure of 73.8 bars (1070 psi). The subcritical extraction is performed in the liquid state at a pressure in the range of 300 to 700 psi (20 to 48 bars) and a temperature or temperatures ranging from 0° to 31°C. The supercritical

extraction is performed in the fluid gas state at a temperature or temperatures above the critical temperature (31.2°C or 89°F) and a pressure in the range of 2000 to 4000 psi (138 to 275 bars). The second new extraction process using supercritical extraction gives a higher yield in a shorter time.

For subcritical extractions, high pressure batch or continuous extraction systems may be used. For supercritical extractions, suitable equipment includes packed or plate columns, towers featuring perforated plates or baffle structures, mixer-settler type equipment equipped with internal mixing elements, and extraction devices utilizing centrifugal force can be used.

As a working example of the second new extraction process, a batch extraction device was used, wherein the material was extracted with liquid carbon dioxide. Drums containing 80 kg of degummed resin from *Boswellia serrata* were charged into a suitable extraction chamber and contacted with liquid carbon dioxide for 2 hours. Each 80 kg charge yielded at least 18 kg of an enriched pasty material containing boswellic acids and other organic acids.

Also within the scope of the present invention is an extract obtained from *Boswellia serrata* obtained with one of the new extraction processes of the present invention. For instance, a total organic acids extract from *Boswellia serrata* can be obtained with the first or second new extraction process of the present invention.

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Claims

1. A composition consisting essentially of, based on the total weight of the composition, β-boswellic acid of at least 12% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 1% by weight and acetyl-11-keto-β-boswellic acid of at least 1% by weight.

2. The composition of claim 1 consisting essentially of, based on the total weight of the composition, β-boswellic acid of at least 14% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 5% by weight and acetyl-11-keto-β-boswellic acid of at least 5% by weight.

3. The composition of claim 1 consisting essentially of, based on the total weight of the composition, β-boswellic acid of 12 to 35% by weight, acetyl-β-boswellic acid of 5 to 35% by weight, 11-keto-β-boswellic acid of 5 to 45% by weight and acetyl-11-keto-β-boswellic acid of 5 to 45% by weight.

4. The composition of claim 3 consisting essentially of, based on the total weight of the composition, β-boswellic acid of 12 to 30% by weight, acetyl-β-boswellic acid of 10 to 25% by weight, 11-keto-β-boswellic acid of 5 to 35% by weight and acetyl-11-keto-β-boswellic acid of 5 to 35% by weight.

5. The composition of claim 4 consisting essentially of, based on the total weight of the composition, β-boswellic acid of 14 to 30% by weight, acetyl-β-boswellic acid of 10 to 20% by weight, 11-keto-β-boswellic acid of 5 to 25% by weight and acetyl-11-keto-β-boswellic acid of 5 to 25% by weight.

6. The composition of claim 3 consisting essentially of, based on the total weight of the composition, β-boswellic acid of 14 to 35% by weight, acetyl-β-boswellic acid of 10 to 20% by weight, 11-keto-β-boswellic acid of 5 to 25% by weight and acetyl-11-keto-β-boswellic acid of 5 to 20% by weight.

7. The composition of claim 3 consisting essentially of, based on the total weight of the composition, β-boswellic acid of 14 to 35% by weight, acetyl-β-boswellic acid of 10 to 20% by weight, 11-keto-β-boswellic acid of 5 to 20% by weight and acetyl-11-keto-β-boswellic acid of 5 to 25% by weight.

8. The composition of claim 1, wherein the β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid are derived from any natural source.

9. A composition comprising three boswellic acids selected from the group consisting of β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid, wherein, based on the total weight of the composition, the amount of β-boswellic acid is at least 5% by weight, the amount of acetyl-β-boswellic acid of is least 5% by weight, the amount of 11-keto-β-boswellic acid is at least 5% by weight, and the amount of acetyl-11-keto-β-boswellic acid is at least 5% by weight.

10. The composition of claim 9, wherein the amount of β-boswellic acid is 14 to 65% by weight, the amount of acetyl-β-boswellic acid is 5 to 65% by weight, the amount of 11-keto-β-boswellic acid is 5 to 60% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 5 to 60% by weight.

11. The composition of claim 10, wherein the amount of β-boswellic acid is 14 to 55% by weight, the amount of acetyl-β-boswellic acid is 10 to 55% by weight, the amount of 11-keto-β-boswellic acid is 5 to 50% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 5 to 50% by weight.

12. The composition of claim 11, wherein the amount of β-boswellic acid is 14 to 35% by weight, the amount of acetyl-β-boswellic acid is 10 to 35% by weight, the amount of 11-keto-β-boswellic acid is 5 to 40% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 5 to 40% by weight.

13. The composition of claim 9, wherein the β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid are derived from any natural source.

14. A composition comprising two boswellic acids selected from the group consisting of β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid, wherein, based on the total weight of the composition, the amount of β-boswellic acid is at least 5% by weight, the amount of acetyl-β-boswellic acid is least 5% by weight, the amount of 11-keto-β-boswellic

acid is at least 5% by weight, and the amount of acetyl-11-keto-β-boswellic acid is at least 5% by weight.

15. The composition of claim 14, wherein the amount of β-boswellic acid is 5 to 95% by weight, the amount of acetyl-β-boswellic acid is 5 to 95% by weight, the amount of 11-keto-β-boswellic acid is 5 to 95% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 5 to 95% by weight.

16. The composition of claim 15, wherein the amount of β-boswellic acid is 30 to 70% by weight, the amount of acetyl-β-boswellic acid is 30 to 70% by weight, the amount of 11-keto-β-boswellic acid is 30 to 70% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 30 to 70% by weight.

17. The composition of claim 16, wherein the amount of β-boswellic acid is 40 to 60% by weight, the amount of acetyl-β-boswellic acid is 40 to 60% by weight, the amount of 11-keto-β-boswellic acid is 40 to 60% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 40 to 60% by weight.

18. The composition of claim 14, wherein the β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid are derived from any natural source.

19. A composition comprising boswellic acids, wherein the boswellic acids consist of three substances selected from the group consisting of β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid, wherein, based on the total weight of the composition, the amount of β-boswellic acid is at least 5% by weight, the amount of acetyl-β-boswellic acid of is least 5% by weight, the amount of 11-keto-β-boswellic acid is at least 5% by weight, and the amount of acetyl-11-keto-β-boswellic acid is at least 5% by weight.

20. The composition of claim 19, wherein the amount of β-boswellic acid is 5 to 65% by weight, the amount of acetyl-β-boswellic acid is 5 to 65% by weight, the amount of 11-keto-β-boswellic acid is 5 to 65% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 5 to 65% by weight.

21. The composition of claim 20, wherein the amount of β-boswellic acid is 15 to 55% by weight, the amount of acetyl-β-boswellic acid is 15 to 55% by

weight, the amount of 11-keto-β-boswellic acid is 15 to 55% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 15 to 55% by weight.

22. The composition of claim 21, wherein the amount of β-boswellic acid is 20 to 40% by weight, the amount of acetyl-β-boswellic acid is 20 to 40% by weight, the amount of 11-keto-β-boswellic acid is 20 to 40% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 20 to 40% by weight.

23. The composition of claim 19, wherein the β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid are derived from any natural source.

24. A composition comprising boswellic acids, wherein the boswellic acids consist of two substances selected from the group consisting of β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid, wherein, based on the total weight of the boswellic acids, the amount of β-boswellic acid is at least 5% by weight, the amount of acetyl-β-boswellic acid of is least 5% by weight, the amount of 11-keto-β-boswellic acid is at least 5% by weight, and the amount of acetyl-11-keto-β-boswellic acid is at least 5% by weight.

25. The composition of claim 24, wherein the amount of β-boswellic acid is 10 to 90% by weight, the amount of acetyl-β-boswellic acid is 10 to 90% by weight, the amount of 11-keto-β-boswellic acid is 10 to 90% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 10 to 90% by weight.

26. The composition of claim 25, wherein the amount of β-boswellic acid is 20 to 80% by weight, the amount of acetyl-β-boswellic acid is 20 to 80% by weight, the amount of 11-keto-β-boswellic acid is 20 to 80% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 20 to 80% by weight.

27. The composition of claim 26, wherein the amount of β-boswellic acid is 30 to 70% by weight, the amount of acetyl-β-boswellic acid is 30 to 70% by weight, the amount of 11-keto-β-boswellic acid is 30 to 70% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 30 to 70% by weight.

28. The composition of claim 27, wherein the amount of β-boswellic acid is 40 to 60% by weight, the amount of acetyl-β-boswellic acid is 40 to 60% by

weight, the amount of 11-keto-β-boswellic acid is 40 to 60% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 40 to 60% by weight.

29. The composition of claim 9, wherein two of the three boswellic acids are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

30. The composition of claim 9, wherein two of the three boswellic acids are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

31. The composition of claim 11, wherein two of the three boswellic acids are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

32. The composition of claim 12, wherein two of the three boswellic acids are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

33. The composition of claim 14, wherein the two boswellic acids are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

34. The composition of claim 15, wherein the two boswellic acids are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

35. The composition of claim 16, wherein the two boswellic acids are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

36. The composition of claim 17, wherein the two boswellic acids are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

37. The composition of claim 19, wherein two of the three substances are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

38. The composition of claim 20, wherein two of the three substances are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

39. The composition of claim 21, wherein two of the three substances are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

40. The composition of claim 22, wherein two of the three substances are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

41. The composition of claim 24, wherein the two substances are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

42. The composition of claim 25, wherein the two substances are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

43. The composition of claim 26, wherein the two substances are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

44. The composition of claim 27, wherein the two substances are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

45. A method for inhibition of DNA, RNA and/or protein synthesis in a human or animal in need of the inhibition, comprising a step of administering a DNA, RNA and/or protein synthesis inhibition effective amount of a composition to said human or animal, wherein the composition comprises β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

46. The method of claim 45, wherein the composition comprises β-boswellic acid of at least 12% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 1% by weight and acetyl-11-keto-β-boswellic acid of at least 1% by weight.

47. The method of claim 46, wherein the composition comprises β-boswellic acid of 12 to 35% by weight, acetyl-β-boswellic acid of 5 to 35% by weight, 11-keto-β-boswellic acid of 5 to 45% by weight and acetyl-11-keto-β-boswellic acid of 5 to 45% by weight.

48. A method for irreversible inhibition of DNA synthesis in a human or animal in need of the inhibition, comprising a step of administering a DNA inhibition effective amount of a composition to said human or animal, wherein the composition comprises β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

49. The method of claim 48, wherein the composition comprises β-boswellic acid of at least 12% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 1% by weight and acetyl-11-keto-β-boswellic acid of at least 1% by weight.

50. The method of claim 49, wherein the composition comprises β-boswellic acid of 12 to 35% by weight, acetyl-β-boswellic acid of 5 to 35% by weight, 11-keto-β-boswellic acid of 5 to 45% by weight and acetyl-11-keto-β-boswellic acid of 5 to 45% by weight.

51. A method for the prevention of a lymphoproliferative disease in a human or animal in need of the prevention, comprising a step of administering a lymphoproliferative disease prevention effective amount of a composition to said human or animal, wherein the composition comprises β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

52. The method of claim 51, wherein the composition comprises β-boswellic acid of at least 12% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 1% by weight and acetyl-11-keto-β-boswellic acid of at least 1% by weight.

53. The method of claim 52, wherein the composition comprises β-boswellic acid of 12 to 35% by weight, acetyl-β-boswellic acid of 5 to 35% by weight, 11-keto-β-boswellic acid of 5 to 45% by weight and acetyl-11-keto-β-boswellic acid of 5 to 45% by weight.

54. The method of claim 51, wherein the lymphoproliferative disease is leukemia or lymphoma.

55. A method for the treatment of a lymphoproliferative disease in a human or animal in need of the treatment, comprising a step of administering a lymphoproliferative disease treatment effective amount of a composition to said human or animal, wherein the composition comprises β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

56. The method of claim 55, wherein the composition comprises β-boswellic acid of at least 12% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 1% by weight and acetyl-11-keto-β-boswellic acid of at least 1% by weight.

57. The method of claim 56, wherein the composition comprises β-boswellic acid of 12 to 35% by weight, acetyl-β-boswellic acid of 5 to 35% by weight, 11-keto-β-boswellic acid of 5 to 45% by weight and acetyl-11-keto-β-boswellic acid of 5 to 45% by weight.

58. The method of claim 55, wherein the lymphoproliferative disease is leukemia or lymphoma.

59. A method for the prevention of an autoimmune disease in a human or animal in need of the prevention, comprising a step of administering an autoimmune disease prevention effective amount of a composition to said human or animal, wherein the composition comprises β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

60. The method of claim 59, wherein the composition comprises β-boswellic acid of at least 12% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 1% by weight and acetyl-11-keto-β-boswellic acid of at least 1% by weight.

61. The method of claim 60, wherein the composition comprises β-boswellic acid of 12 to 35% by weight, acetyl-β-boswellic acid of 5 to 35% by weight, 11-keto-β-boswellic acid of 5 to 45% by weight and acetyl-11-keto-β-boswellic acid of 5 to 45% by weight.

62. The method of claim 59, wherein the autoimmune disease is psoriasis, sarcoidosis, systemic lupus erythematosis, Grave's disease, Hashimoto's thyroiditis, silent thyroiditis, Crohn's disease, Goodpasture syndrome, insulin-dependent diabetes mellitus, insulin-resistant diabetes mellitus, myasthenia gravis, Addison's disease, idiopathic hypoparathyroidism, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, rheumatoid arthritis or scleroderma.

63. A method for the treatment of an autoimmune disease in a human or animal in need of the treatment, comprising a step of administering an autoimmune disease treatment effective amount of a composition to said human or animal, wherein the composition comprises β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

64. The method of claim 63, wherein the composition comprises β-boswellic acid of at least 12% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 1% by weight and acetyl-11-keto-β-boswellic acid of at least 1% by weight.

65. The method of claim 64, wherein the composition comprises β-boswellic acid of 12 to 35% by weight, acetyl-β-boswellic acid of 5 to 35% by

weight, 11-keto-β-boswellic acid of 5 to 45% by weight and acetyl-11-keto-β-boswellic acid of 5 to 45% by weight.

66. The method of claim 63, wherein the autoimmune disease is psoriasis, sarcoidosis, systemic lupus erythematosis, Grave's disease, Hashimoto's thyroiditis, silent thyroiditis, Crohn's disease, Goodpasture syndrome, insulin-dependent diabetes mellitus, insulin-resistant diabetes mellitus, myasthenia gravis, Addison's disease, idiopathic hypoparathyroidism, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, rheumatoid arthritis or scleroderma.

67. A process of obtaining a total organic acids extract from *Boswellia serrata*, wherein the total organic acids extract comprises boswellic acids, said process comprising the following steps:

(1) providing a *Boswellia serrata* component;

(2) extracting the component with a C_1-C_6 alcohol to obtain an alcohol extract;

(3) removing the C_1-C_6 alcohol from the alcohol extract to obtain a liquid;

(4) treating the liquid with an alkaline substance to obtain an alkaline liquid;

(5) washing the alkaline liquid with an organic solvent;

(6) removing the organic solvent to obtain an aqueous liquid; and thereafter

(7) treating the aqueous liquid with an acid to obtain the total organic acids extract as a precipitate.

68. The process of claim 67, wherein the *Boswellia serrata* component is the gum from *Boswellia serrata*.

69. The process of claim 67, wherein the C_1-C_6 alcohol in step (2) is isopropyl alcohol.

70. The process of claim 67, wherein said alkaline substance is KOH and said liquid in step (4) is treated with KOH at pH>9.5.

71. The process of claim 67, wherein said aqueous liquid in step (7) is treated with hydrochloric acid at about pH 3 to 4 to obtain the precipitate.

72. The process of claim 67, wherein the precipitate is washed with water and dried at a temperature less than about 50°C.

73. The process of claim 67, wherein the organic solvent is ethyl acetate.

74. A total organic acids extract from *Boswellia serrata* obtained by the process of claim 67.

75. A process of obtaining boswellic acids comprising the following steps:

(a) providing a *Boswellia serrata* component;

(b) extracting said *Boswellia serrata* component with carbon dioxide to obtain a fluid extract; and

(c) removing carbon dioxide from the fluid extract to obtain the boswellic acids.

76. The process of claim 75, wherein the *Boswellia serrata* component is a gum from *Boswellia serrata*.

77. The process of claim 75, wherein the extracting in step (b) is performed with subcritical extraction.

78. The process of claim 75, wherein the extracting in step (b) is performed with supercritical extraction.

79. A method for the treatment of a tumor in a human or animal in need of the treatment by administering a tumor treating effective amount of a composition to said human or animal, wherein the composition comprises β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

80. The method of claim 79, wherein the composition comprises β-boswellic acid of at least 12% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 1% by weight and acetyl-11-keto-β-boswellic acid of at least 1% by weight.

81. The method of claim 80. wherein the composition comprises β-boswellic acid of 12 to 35% by weight, acetyl-β-boswellic acid of 5 to 35% by weight, 11-keto-β-boswellic acid of 5 to 45% by weight and acetyl-11-keto-β-boswellic acid of 5 to 45% by weight.

82. A method of inhibiting the synthesis of DNA. RNA and/or protein in a human or animal in need of the inhibition. comprising administering a DNA, RNA and/or protein synthesis inhibition effective amount of β-boswellic acid, acetyl-β-boswellic acid. 11-keto-β-boswellic acid or acetyl-11-keto-β-boswellic acid.

83. A method for irreversibly inhibiting the synthesis of DNA in a human or animal in need of the inhibition. comprising administering a DNA synthesis inhibition effective amount of β-boswellic acid. acetyl-β-boswellic acid. 11-keto-β-boswellic acid or acetyl-11-keto-β-boswellic acid.

84. A method for preventing or treating a lymphoproliferative disease in a human or animal in need of the prevention or treatment, comprising administering a lymphoproliferative disease preventing or treating effective amount of β-boswellic acid, acetyl-β-boswellic acid. 11-keto-β-boswellic acid or acetyl-11-keto-β-boswellic acid.

85. A method for preventing or treating an autoimmune disease in a human or animal in need of the prevention or treatment. comprising administering an autoimmune disease preventing or treating effective amount of β-boswellic acid, acetyl-β-boswellic acid. 11-keto-β-boswellic acid or acetyl-11-keto-β-boswellic acid.

Figure 1

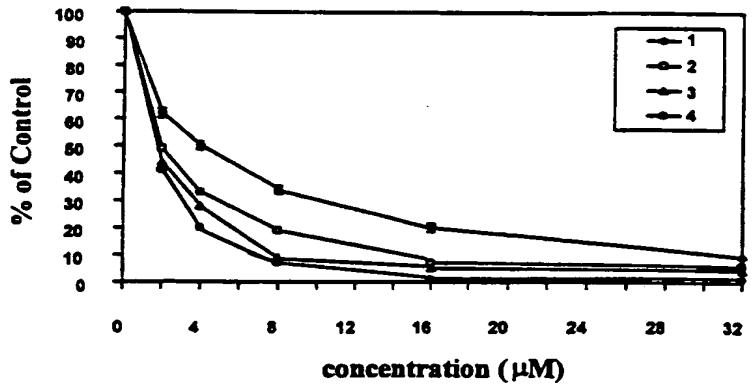


Figure 2

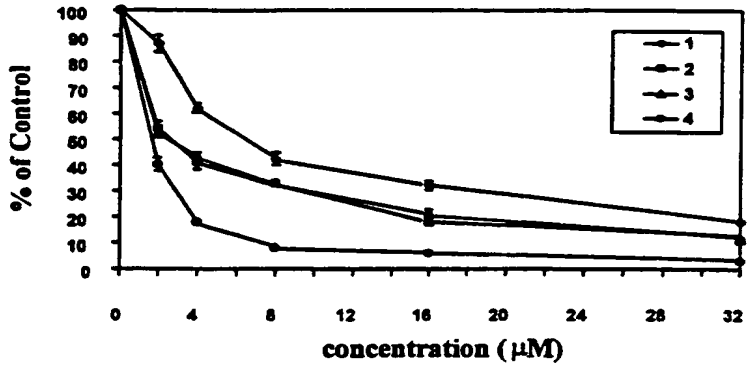


Figure 3

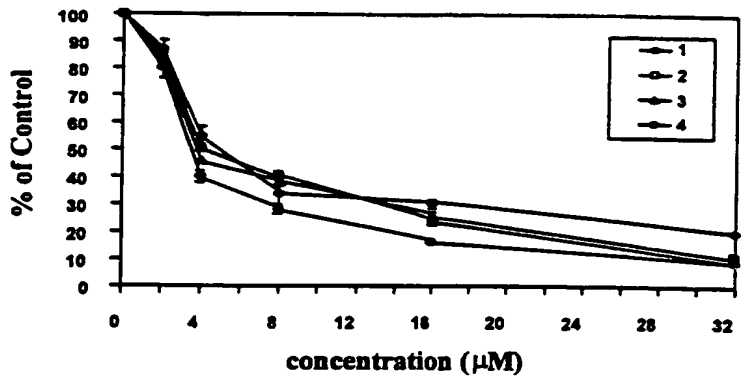

100
90
80
70
60
50
40
30
20
10
0
% of Control
0
4
8
12
16
20
24
28
32
concentration (μM)
1
2
3
4

Figure 4

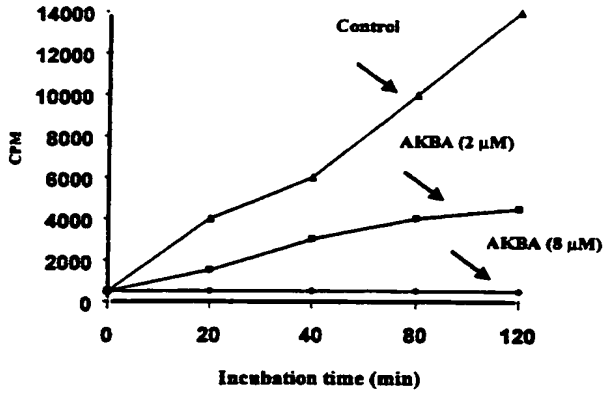

14000
12000
10000
8000
6000
4000
2000
0
CPM
Control
AKBA (2 µM)
AKBA (8 µM)
0
20
40
80
120
Incubation time (min)

Figure 5 : β–Boswellic acids Content in Commercial Samples of *Boswellia serrata* extract as determined by HPLC

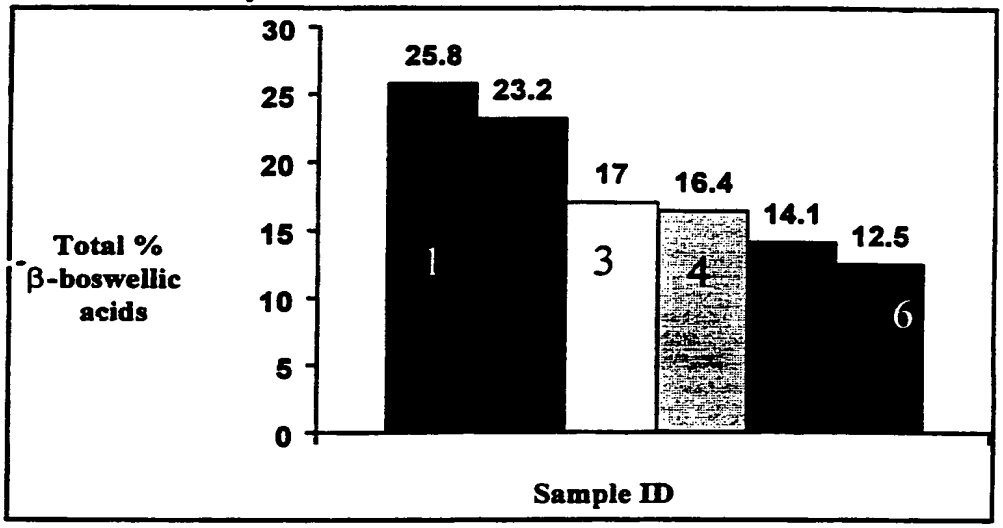


Figure 6 : β–Boswellic acids Composition in Commercial Samples of *Boswellia serrata* extract as determined by HPLC

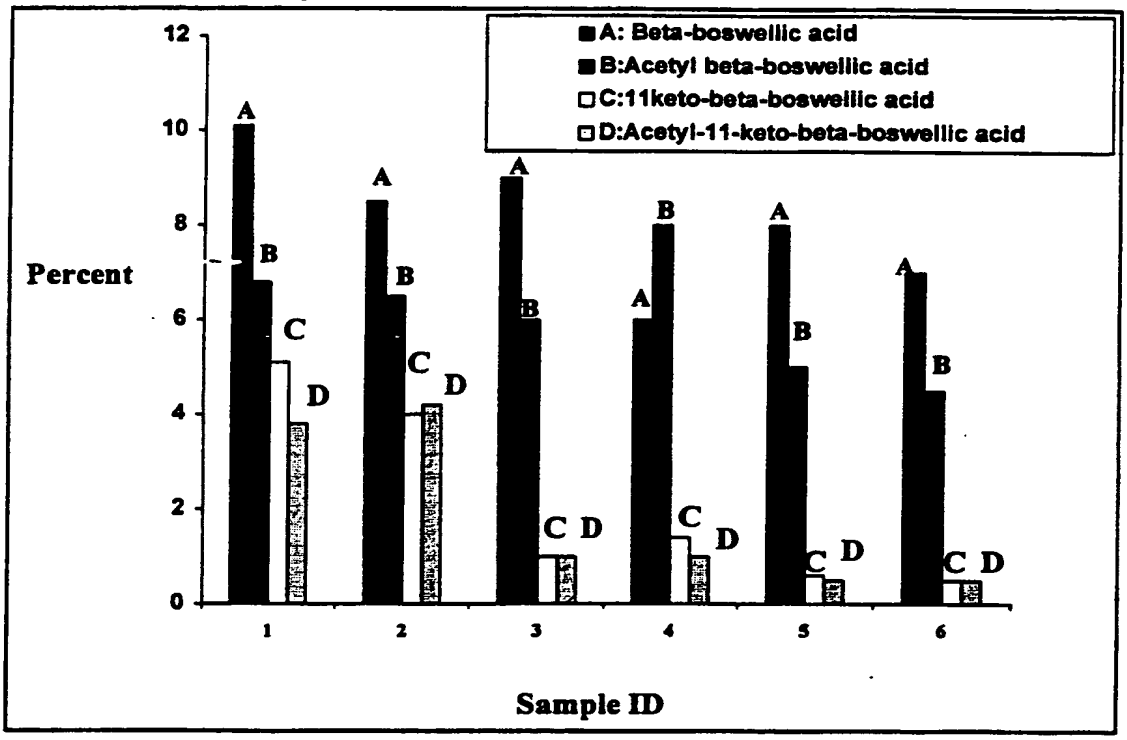
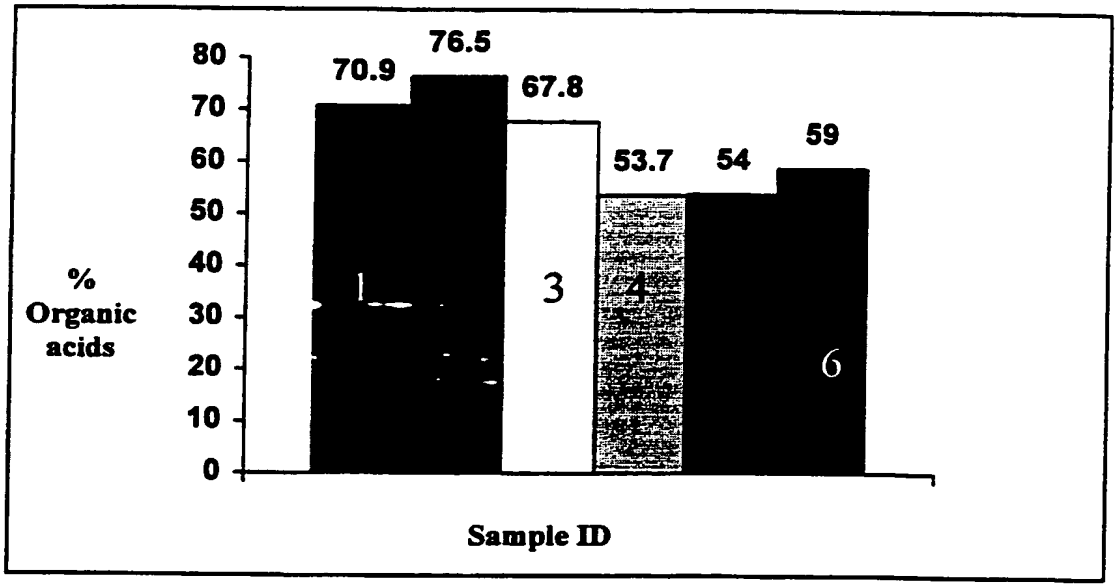


Figure 7: Total Organic Acids in Commercial Samples of *Boswellia serrata* extract as determined by titration



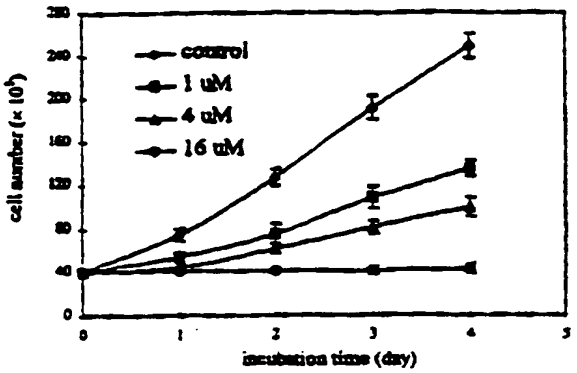


FIG. 8

Inhibitory effect of compound 4 on the growth of HL-60 cells. Results represent the average values for three experiments each performed in triplicate. Significantly different from control, $P < 0.05$.

INTERNATIONAL SEARCH REPORT

International Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/19 A61P35/00 A61P35/02 A61P37/06 A61K35/78

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, EMBASE, BIOSIS, WPI Data, MEDLINE, CHEM ABS Data, SCISEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	EP 0 552 657 A (AMMON HERMANN P T) 28 July 1993 (1993-07-28) page 5, line 30 -page 6, line 28 claims 1,2	1-44, 59-78
X	PATENT ABSTRACTS OF JAPAN vol. 017, no. 100 (C-1030), 26 February 1993 (1993-02-26) & JP 04 288095 A (TSUMURA & CO), 13 October 1992 (1992-10-13) abstract	1-44, 59-78

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
4 September 2000	15/09/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bonzano, C

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/08217

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

In tional Application No
PCT/US 00/08217

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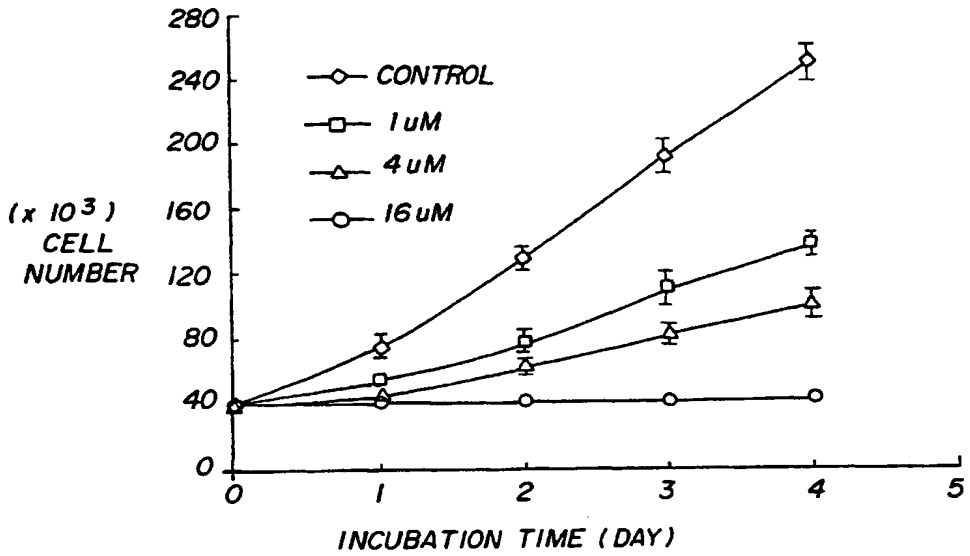
[Continued on next page]

(54) Title: COMPOSITIONS OF BOSWELLIC ACIDS DERIVED FROM BOSWELLIA SERRATA GUM RESIN, FOR TREATING LYMPHOPROLIFERATIVE AND AUTOIMMUNE CONDITIONS



(57) Abstract: Method of treatment of lymphoproliferative and autoimmune disorders with a new composition of four boswellic acids including β-boswellic acid, 3-O-acetyl-β-boswellic acid, 11-keto-β-boswellic acid, and 3-O-acetyl-11-keto-β-boswellic acid. Boswellic acids of invention have been obtained in a novel industrial process from the gum resin of Boswellia serrata tree, providing standardized composition which inhibits DNA, RNA and protein synthesis of the target cell without cytotoxic effects. Composition of invention provides advantage of irreversible cytostatic therapy, equivalent to biological effects of a cytotoxic therapy without killing body cells.

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COMPOSITIONS OF BOSWELLIC ACIDS DERIVED FROM BOSWELLIA SERRATA GUM RESIN, FOR TREATING LYMPHOPROLIFERATIVE AND AUTOIMMUNE CONDITIONS

Background of the Invention

The present invention concerns new compositions of boswellic acids, methods of using the compositions or individual boswellic acids to treat lymphoproliferative and autoimmune conditions, and two new methods of isolating the new compositions.

Boswellia serrata (N.O. Burseraceae) is a large, branching, deciduous tree which grows abundantly in the dry, hilly parts of India. It is known as "Dhup", Indian Frankincense or Indian Olibanum. The gum resin exudate of *Boswellia serrata*, known in the vernacular as "Salai guggal", has been used in the Ayurvedic system of medicine for the management of rheumatism, respiratory diseases, and liver disorders. The major use of *Boswellia serrata* in contemporary medicine is as an anti-arthritic and anti-inflammatory pharmacological agent.

The active principles of the gum resin, boswellic acids, emerge as leading non-steroidal, anti-inflammatory compounds (drugs) NSAID with broad biological activities and low ulcerogenic index. Preclinical studies established that an alcoholic extract of the gum resin displayed marked anti-inflammatory activity in mice and rats, and also inhibited the formation of leukotrienes in rat peritoneal neutrophils *in vitro*. Boswellic acids decreased the formation of inflammatory leukotriene B4 (B4 is an outcome of the arachidonic acid metabolism) in rat peritoneal neutrophils in a dose-dependent way with IC50 values ranging from 1.5 to 7uM. The anti-inflammatory mechanism of action of boswellic acids inhibited the leukotriene synthesis via 5-lopoxygenase, but did not affect the 12-lipoxygenase and cyclooxygenase activity. Additionally, boswellic acids did not impair the peroxidation of arachidonic acid by iron and ascorbate. These results suggest that boswellic acids are specific, non-redox inhibitors of leukotriene synthesis either interacting with 5-lipoxygenase or blocking its translocation.

Safayhi, H. et al (1992) established and prior art by Ammon et al (EP 0 552 657) teaches that six boswellic acids are involved in the inhibition of 5-lipoxygenase, thus potentially blocking synthesis of inflammatory leukotrienes and thus useful in treatment of clinical conditions like inflammatory bowel diseases, arthritis, asthma, psoriasis and chronic form of hepatitis. These six compounds listed by Ammon in order of their

biological strength based on IC50-values are as follows: 1. acetyl-11-keto-beta-boswellic acid. 2. Beta-boswellic acid. 3. 11-keto-beta-boswellic acid. 4. Alpha-boswellic acid. 5. Acetyl-beta-boswellic acid and 6. Acetyl-alpha-boswellic acid. Ammon et al (WO 97/07796) also teaches that boswellic acids can be also used as inhibitor of elevated leucocyte elastase or plasmin activity and useful in clinical conditions characterized by the elevated activity of the elastase and/or plasmin. The anti-inflammatory properties of the gum resin is attributed to the presence of "boswellic acids". Boswellic acids were found to inhibit two pro-inflammatory enzymes, 5-lipoxygenase (which generates inflammatory leukotrienes) and Human Leukocyte Elastase (HLE). HLE is a serine protease which initiates injury to the tissues. which in turn triggers the inflamation. Studies by Safayhi. H. et al (1997) showed that Acetyl-11-keto-β-boswellic acid decreased the activity of human leukocyte elastase (HLE) *in vitro* with an IC_{50} value of about 15 μM.

Prior art by Lee Yue-Wei et al (U.S. Patent No. 5,064,823) also teaches that pentacyclic triterpenoid compounds such as alpha boswellic acid and its acetate, beta boswellic acid and its acetate have an inhibitory effect on topoisomerase I and topoisomerase II which according to authors may result in increased cancer cell differentiation. That process may be considered a cancer treatment modality.

An alcoholic extract of the gum resin was examined for anti-carcinogenic properties by Mukherji S. et al (1970). When tested on mice with Ehrlich ascites carcinoma and S-180 tumor. the extract inhibited tumor growth and increased the life span of experimental animals with carcinoma.

Summary of the Invention

Despite recognized potential of boswellic acids as NSAIDs and as a promising cancer fighting compounds. there are two major obstacles which stand in way of utilization boswellic acids in the health care: (a) poorly understood relationships between structure/composition of boswellic acids and their biological utility, and (b) lack of the boswellic acids product standardized on the basis of clearly defined structure function claim.

In the present invention. four purified boswellic acids. individually or in mixtures. were discovered to be effective in treating lymphoproliferative conditions

and autoimmune diseases in animals, including humans. The four purified boswellic acids were shown, in the present invention, in studies to evaluate the effects against macromolecular biosynthesis and cellular growth of human leukemia HL-60 cells. The four major pentacyclic triterpenic (boswellic) acids present in the acidic extract of *Boswellia serrata* gum in the present invention are:

- β–Boswellic Acid (I)
- Acetyl-β–Boswellic Acid (II)
- 11-keto-β–Boswellic Acid (III)
- Acetyl-11-keto-β–Boswellic Acid (IV)

Figures 1, 2, and 3 show the inhibitory effects of compounds I-IV on the DNA, RNA and protein synthesis of HL-60 cells, respectively (in Fig. 1-3, lines 1, 2, 3 and 4 refer to the data of compounds I, II, III and IV, respectively). Tables 1 and 2 show the inhibitory effect of a "total organic acids" extract of the exudate of *Boswellia serrata* on DNA, RNA and protein synthesis or growth in HL-60 cells. Table 3 shows the inhibitory effect of the "total organic acids" extract of the exudate of *Boswellia serrata* on the incorporation of [^{3}H]thymidine into the DNA of HL-60 cells. The initial rates of incorporation of [^{3}H]-thymidine, [^{3}H]-uridine and [^{3}H]-leucine into trichloroacetic acid (TCA)-insoluble material were utilized to estimate the rates of DNA, RNA, and protein synthesis, respectively, in HL-60 cells. All of the inhibitory effects of compounds I-IV and the alcoholic extract on DNA, RNA and protein synthesis of HL-60 cells were in a dose-dependent manner. Compounds I, II, III and IV exhibited 50% inhibitory activity on the incorporation of [3H]-thymidine into DNA at concentrations of 3.7, 1.4, 0.9 and 0.6 μM, respectively, the incorporation of [3H]-uridine at concentrations of 7.1, 2.3, 2.2 and 0.5 μM, respectively, and the incorporation of [3H]-leucine into protein at concentrations of 6.3, 5.4, 5.1 and 4.1 μM, respectively, in cultured HL-60 cells incubated for 2 hours.

Comparison of the IC50 values indicated that the order of inhibitory activity for compounds I-IV is IV>III>II>I. This observation is a principle behind the new composition of boswellic acids effective in lymphoproliferative and autoimmune disorders. The discovered relationship between structure and activity of specific boswellic acids in inhibition of DNA, RNA and protein synthesis has not been

previously reported. Our research has determined for the first time that (1) 11-keto group of boswellic acids is a principal moiety for the above described biological activity, and (2) 3-0-acetyl group amplifies that activity further resulting in a predictable cytostatic and immunomodulatory effects of boswellic acids.

It has been further determined that compound IV, which induced the most pronounced inhibitory effects on DNA, RNA and protein synthesis in HL-60 cells, had an irreversible inhibitory action on DNA synthesis. In this experiment HL-60 cells were preincubated with compound IV at 2 and 8 μM for 30 min at 37°C, washed with phosphate buffer saline and [3H]-thymidine was added to the culture. At desired times, the reactions were terminated and the rates of DNA synthesis were determined. The results (Fig. 4) showed that the inhibitory effect on DNA synthesis was still dependent upon the concentrations of compound IV and identical to that without washing. This finding suggested that the inhibitory action of compound IV on DNA synthesis was irreversible.

The effect of compound IV on cellular growth of HL-60 cells was tested. As shown in Fig. 8, compound IV depressed the growth of HL-60 cells in a dose-dependent manner. Addition of compound IV at 1, 4, or 16 μM to HL-60 cells and incubation at 37°C for 4 days inhibited the cellular growth by 54.5, 71.8 or 98.6%. In order to test whether this growth was the result of cell cytotoxicity, the effects of this compound on cell viability were examined after 4 days incubation using the trypan blue exclusion method. The cells viability at concentrations of 0, 1, 4, 16 μM were 97.0, 96.8, 96.5, or 96.7%, respectively.

This experiment showed that compound IV at the concentrations which significantly inhibited cell growth, did not affect cell viability. These results indicated that inhibition of the cell growth is due to the cytostatic rather then cytotoxic effects. The inhibition of cell proliferation can be explained by its interference with biosynthesis of DNA, RNA and protein all of which are required for cell proliferation. These results for the first time establish that composition of boswellic acid enriched with the compound IV can be used as cytostatic and immunomodulatory preparation, due to its profound and well defined effect on myeloid cell metabolism.

Within the scope of the present invention are methods of preventing or treating lymphoproliferative disorders or autoimmune diseases by administering a composition comprising a "total organic acids" extract obtained from *Boswellia serrata*, administering compound I, II, III or IV individually or administering a mixture comprising two, three or all four of compounds I, II, III and IV in humans or animals in need of such a prevention or treatment. Also within the scope of the present invention are methods of preventing or treating tumors or inflammatory disorders by administering the composition comprising the "total organic acids" extract obtained from *Boswellia serrata* or administering compound I, II, III or IV individually or administering a mixture comprising two, three or all four of compounds I, II, III and IV in humans or animals in need of such a prevention or treatment. The present invention also includes the composition comprising the "total organic acids" extract obtained from *Boswellia serrata*, a composition comprising two, three or four of compounds I-IV and two processes of obtaining boswellic acids or of obtaining the composition comprising the "total organic acids" extract obtained from *Boswellia serrata*.

The lymphoproliferative disorders that can be treated with the methods of using boswellic acids of the present invention include leukemia and lymphoma. Leukemia that can be treated by the methods of the present invention include myeloid leukemia, acute myelogenous leukemia, acute lymphocytic leukemia, acute non-lymphocytic leukemia, chronic lymphocytic leukemia, and hairy cell leukemia. The autoimmune diseases that can be treated with the methods of using boswellic acids of the present invention include, for example, psoriasis, sarcoidosis, systemic lupus erythematosis, Graves' disease, Hashimoto's thyroiditis, silent thyroiditis, Crohn's disease, Goodpasture syndrome, insulin-dependent diabetes mellitus, insulin-resistant diabetes mellitus, myasthenia gravis, Addison's disease, idiopathyic hypoparathyroidism, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, rheumatoid arthritis, and scleroderma. The methods of using boswellic acids of the present invention are also effective in treating tumors, including, for example, breast tumors, ovarian tumors, uterine tumor, lung tumors, liver tumors,

renal tumors, prostatic tumors, pancreatic tumors, tumors of the gastrointestinal tract, e.g. colorectal tumors, brain tumors, and head and neck tumors.

The following tables present data concerning the biological effects of an alcoholic extract of the exudate of *Boswellia serrata*. Table 1 below presents data on the effects of the alcoholic extract of the exudate of *Boswellia serrata* on the DNA synthesis, RNA synthesis and protein synthesis in HL-60 cells in culture.

Table 1

BSE added	DNA synthesis		RNA syntheses		Protein synthesis	
(μm)	% Control	% Inhibition	% Control	% Inhibition	% Control	% Inhibition
0	100	0	100	0	100	0
0.75	80	20	91	9	70	30
1.5	45	55	64	36	52	48
3.0	35	65	62	38	26	74
6.0	23	77	20	80	12	88
12.0	19	81	10	90	9	91
25.0	18	82	8	92	8	92

Various concentrations of the *Boswellia serrata* extract, as indicated above, were added to 1 mL of HL-60 cells suspended in RPMI medium. [^{3}H]thymidine (50 μCi/μmol: 3 mL), [^{3}H]uridine (55 μCi/μmol: 5 μL), [^{3}H]leucine (200 μCi/μmol: 10 μL), were added to the cell suspension and incubated at 37°C for 120 min. Reactions were terminated by addition of 3 mL of cold PBS, and the rates of DNA, RNA, and protein synthesis were determined.

Table 2 below presents data on the effect of the alcoholic extract of the exudate of *Boswellia serrata* on the growth of HL-60 cells in culture. The alcoholic extract of the exudate of *Boswellia serrata* inhibited the growth of HL-60 cells in a concentration dependent fashio.

Table 2

Incubation time (hours)	Concentration of BSE (μM)			
	0	4	12	50
0	25 ± 2.3	25 ± 2.3	25 ± 2.3	25 ± 2.3
24	45 ± 2.1	40 ± 4.2 (25%)	39 ± 3.7 (30%)	30 ± 4.0 (75%)
48	71 ± 1.5	66 ± 4.7 (11%)	57 ± 3.5 (30%)	27 ± 2.0 (97%)
72	102 ± 2.1	95 ± 2.9 (9%)	72 ± 7.8 (40%)	25 ± 1.2 (100%)
96	166 ± 16.6	159 ± 11 (5%)	102 ± 2.6 (45%)	31 ± 2.2 (96%)

Various concentrations of BSE, as indicated above, were added to the HL-60 cell cultures. These cultures were counted daily using a hemacytometer under a microscope with 10x magnification every 24 hours. Data are expressed as the mean = SE calculated from triplicate studies. Data in parentheses are the percent inhibition of cell growth.

Other than the inhibitory effects on the synthesis of RNA and protein in HL-60 cells grown in culture, the present invention demonstrated that boswellic acids have an inhibitory effect on DNA synthesis in HL-60 cells. Table 3 below shows that the alcoholic extract of the exudate of *Boswellia serrata* can inhibit DNA synthesis in HL-60 cells as demonstrated by an inhibition of the incorporation of ^{3}H-labeled thymidine into the DNA of HL-60 cells. Similar to the results in Table 2, Table 3 demonstrates that the inhibitory effect of the alcoholic extract of the exudate of *Boswellia serrata* on DNA synthesis in HL-60 cells exhibited a concentration dependent response.

Table 3

Incubation time	Concentration of BSE (μM)			
(min)	0	4	12	50
		(cpm/5 x 10^5 cells)		
0	279 ± 76	352 ± 114	312 ± 54	225 ± 15
120	11112 ± 1897	4039 ± 737	2794 ± 306	1893 ± 505
		(69%)	(77%)	(86%)

[^{3}H]Thymidine (3 μL; 50 μCi/μmol), vehicle or various concentrations of BSE in vehicle were added to 1 mL of HL-60 cells (5 x 10^5 cells/mL) in culture, and the cultures were incubated at 37°C for 120 min. Data are expressed as the mean ± SE calculated from triplicate studies. Data in parentheses are the percent inhibition of [^{3}H]thymidine incorporation into the DNA of HL-60 cells.

Brief Description of the Drawings

Fig. 1 depicts the effects of compounds I-IV on the DNA synthesis in HL-60 cells.

Fig. 2 depicts the effects of compounds I-IV on the RNA synthesis in HL-60 cells.

Fig. 3 depicts the effects of compounds I-IV on the protein synthesis in HL-60 cells.

Fig. 4 shows the inhibitory effects of compound IV on the DNA synthesis in HL-60 cells.

Fig. 5, 6 and 7 show the β-boswellic acids contents in 6 commercial samples of *Boswellia serrata* extract.

Fig. 8 shows the inhibitory effect of compound IV on the growth of HL-60 cells.

Detailed Description of the Invention

Based on our experimental data on relationship between structure and function of the four boswellic acids of invention, a novel manufacturing and standardization process for boswellic acids have been developed. The new

standardization process resulted in changes in the nomenclature of the boswellic acids preparation. The new nomenclature included the following changes.

The phrase "total organic acids" from *Boswellia serrata* refers to an organic acid fraction of an extract of *Boswellia serrata* or *Boswellia serrata* gum. The "total organic acids" from *Boswellia serrata* constitute approximately 65-70%, by weight, of the total alcoholic extract of *Boswellia serrata*. In the methods of treatment of the present invention, the daily effective dose, for a 70 kg subject to be treated, is 1-5000 mg "total organic acids" from *Boswellia serrata*, 2 to 4 times a day. The preferred daily effective dose is 10-500 mg "total organic acids", 2 to 4 times a day. The more preferred daily effective dose is 100-400 mg "total organic acids", 2 to 4 times a day. The most preferred daily effective dose is 200 mg "total organic acids", 3 times a day. For humans or animals of a body weight other than 70 kg, the above doses can be adjusted accordingly based on the body weight or the body surface area based on methods known in the art.

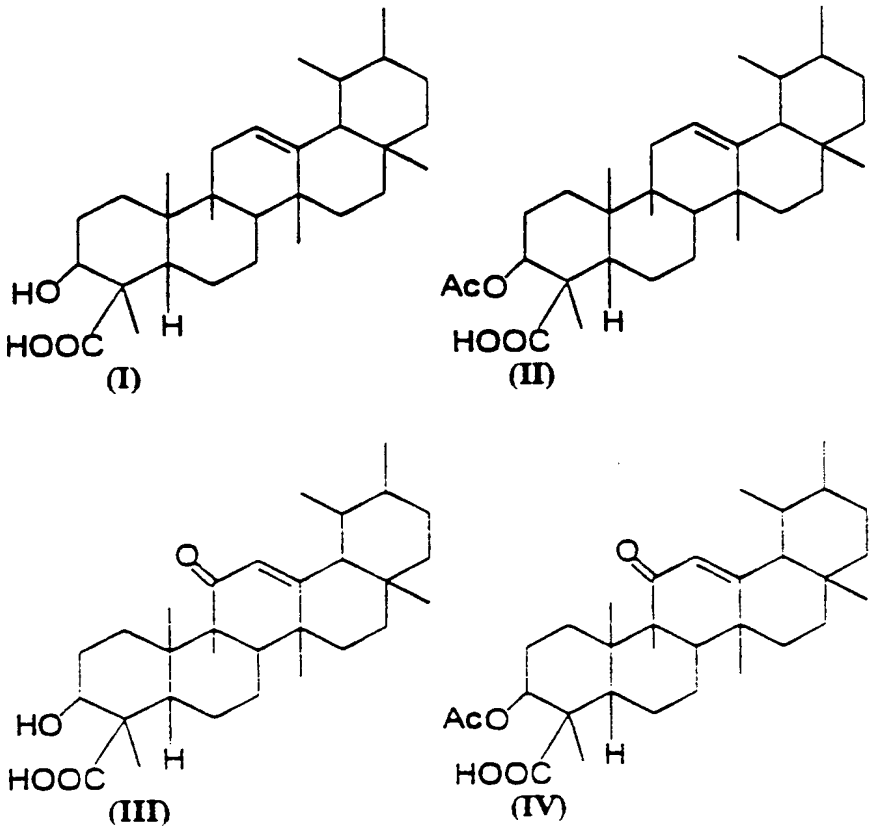
The term "pure boswellic acids" indicates the four major boswellic acids in each dosage form. The "pure boswellic acids" can contain two, three or all four of the four major boswellic acids, i.e. β-boswellic acid (I), acetyl-β-boswellic acid (II), 11-keto-β-boswellic acid (III), and acetyl-11-keto-β-boswellic acid (IV). The "pure boswellic acids" constitute approximately 25% of the "total organic acids". In the methods of treatment of the present invention, the daily effective dose, for a 70 kg subject to be treated, is 0.25-1250 mg "pure boswellic acids", 2 to 4 times a day. The preferred daily effective dose is 2.5-125 mg "pure boswellic acids", 2 to 4 times a day. The more preferred daily effective dose is 25-100 mg "pure boswellic acids", 2 to 4 times a day. The most preferred daily effective dose is 50 mg "pure boswellic acids", 3 times a day. For humans or animals of a body weight other than 70 kg, the above doses can be adjusted accordingly based on the body weight or the body surface area based on methods known in the art.

The total organic acids extract from *Boswellia serrata* can be administered by topical, inhalational, parenteral or oral routes, or by nasal spray or suppositories. Similarly, pure boswellic acids, individual boswellic acids, or mixtures thereof, can

be administered by topical, inhalational, parenteral or oral routes, or by nasal spray or suppositories.

Although there are other components in the Boswellii serrata gum (e.g. alpha and gamma-Boswellic acids), the four major pentacyclic triterpenic (boswellic) acids present in the acidic extract of *Boswellia serrata* gum of the invention used for standardization are:

- β–Boswellic Acid (I)
- Acetyl-β–Boswellic Acid (II)
- 11-keto-β–Boswellic Acid (III)
- Acetyl-11-keto-β–Boswellic Acid (IV)



Commercial samples of *Boswellia serrata* extracts vary greatly in their contents of boswellic acids, which limits, as previously mentioned, a reliable use of boswellic acids in medical and veterinary applications. The analytical results for six commercial samples are indicated in Figure 5, Figure 6 and Figure 7, in terms of content of boswellic acids, their composition, and total organic acids content respectively. In many commercial samples, the most active β-Boswellic acids are available in negligible quantities only. The total organic acids content in these samples as determined by titration is indicated in Figure 7.

The above analytical results make it evident that (a) there is need for accurately standardized boswellic acid product by the HPLC method, and (b) that the active components in *Boswellia serrata* extract cannot be accurately predicted based on titrimetric method analysis. It is equally interesting to note that while the titrimetric method gives more than 50% by weight of organic acids, several of the commercially available products contain only negligible amounts of the two key boswellic acids, namely 11- keto- beta- and acetyl- 11- keto- beta- boswellic acids (Figure 6).

Method of extraction of boswellic acids

By applying a prior art extraction method on a typical sample of *Boswellia serrata*, a composition was obtained containing the four boswellic acids, compounds I-IV, at concentrations shown below:

Component	**% by weight**
I. β–Boswellic Acid	10.1
II. Acetyl-β–Boswellic Acid	6.8
III. 11-keto-β–Boswellic Acid	5.1
IV. Acetyl-11-keto-β–Boswellic Acid	3.8
Total	**25.8**

The "total organic acids" value of this preparation by titration method was: 70.9% by weight.

The present invention includes a first new process of extraction to obtain boswellic acids to ascertain a minimum yield of total boswellic acids by HPLC of minimum 38 weight%, with compound IV of not less than 4 weight%, compound III

of not less than 5 weight%, compound II of not less than 10 weight% and compound I of not less than 14 weight%. The yield of boswellic acids obtainable by the first new process of the present invention is much higher than the prior art process of extraction. Flow chart of old process versus the first new extraction and manufacturing process is shown below.

PROCESS COMPARISON

OLD PROCESS	NEW PROCESS
1. *Boswellia serrata*	1. *Boswellia serrata*
2. Extract with hot isopropyl alcohol	2. Extract with hot C_1-C_6 alcohol, e.g. isopropyl alcohol, butanol
3. Concentrate the isopropyl alcohol extract to 50%	3. Strip off the alcohol extract completely
4. Treat with KOH to pH 9.5 at 60°C	4. Treat with an alkaline substance, e.g. alkali such as KOH or NaOH, to pH>9.5 at room temperature
5. Remove isopropyl alcohol and wash with ether	5. Wash with an organic solvent, such as an ester or ketone solvent
6. Treat aqueous layer with hydrochloric acid to pH 4	6. Treat aqueous layer with hydrochloric acid to pH 4
7. Obtain precipitate	7. Obtain precipitate
8. Wash precipitate with water	8. Wash precipitate with water
9. Dry the precipitate	9. Dry the precipitate at <50°C

In the first new process of extraction to obtain boswellic acids, an example of the organic solvent used in step 5 is ethyl acetate. As needed, modifications, obvious to one skilled in the art, of the new process of extraction to obtain boswellic acids can be done. The modified new process of extraction is also within the scope of the present invention.

Example of manufacturing process of boswellic acid of invention

Process Data Sheet For The Manufacture Of Boswellin 100 kg

1. Charge the extractor with Boswellia serrata gum 555 kg.
2. Charge isopropyl alcohol to the soaking level (1100L-false bottom capacity).

3. Pass steam into the jacket and maintain the temperature at 68-70 deg. C in the core body of the reactor.
4. Drain the extract into a reactor and concentrate at 70 deg. C to strip off isopropyl alcohol completely.
5. Charge isopropyl alcohol to the soaking level 550 L and repeat the step 3 to 4
6. Repeat step 5
7. Charge 560 L of 5 weight% aqueous KOH. then stir at room temperature for 3 hours.
8. Wash with ethyl acetate 830 L.
9. Drain the ethyl acetate layer and collect aqueous layer.
10. Repeat step 8 and 9 two times with 550 L ethylacetate and collect the aqueous layer.
11. Charge the aqueous layer (from steps 9 and 10) into a reactor.
12. Add slowly 6 N HCl to pH 3-4 (~30L) while stirring at room temperature.
13. Forms a precipitate.
14. Add 1000L of water and let it stand at room temperature for 8 hours (or less depending on the observation).
15. Collect the precipitate (by draining into a nutsch and scooping), wash with water.
16. Check for Boswellin in aqueous portion. if absent discard.
17. Dry the prcipitate not above 50 deg. C.
18. Yield expected ~ 100 kg (assay by HPLC 38-40%).

Assay by HPLC for Beta Boswellic acids

Mobile phase:

Mobile phase A: 1000 ml of Acetonitrile with 0.05ml (1 drop) of glacial acetic acid. filter and degas.

Mobile phase B: Mix water and acetonitrile in the ratio150:850 with 0.05ml(1 drop) of glacial acetic acid filter and degas.

Use gradient program

Time	A concentration	B concentration
0 min	90%	10%

15 min	20%	80%
20 min	0%	100 %
25 min	50%	50%
30min	100%	0%
30min	stop	

Sample preparation:

Weigh accurately about 200 mg of the sample and transfer into a 50ml volumetric flask. Add 25 ml of methanol to dissolve the sample. and sonicate for 3 minutes, dilute to volume. mix.

Standard preparation:

1. Beta-boswellic acid: weigh accurately about 25 mg of the standard and transfer into a 10 ml volumetric flask. Add 5 ml of methanol to dissolve the sample, sonicate for 3 minutes. dilute to volume, mix.
2. Acetyl-beta-boswellic acid: weigh accurately about 500 mg of standard and transfer into a 10 ml volumetric flask. Add 5 ml of methanol to dissolve the sample, sonicate for 3 minutes, dilute to volume, mix.
3. 11-Keto-beta-boswellic acid; weigh accurately about 25 mg of the standard and transfer into a 25 ml volumeric flask. Add 15 ml of methanol to dissolve the sample. sonicate for 3 minutes. dilute to volume, mix.
4. Acetyl-11-keto-beta-boswellic acid: weigh accurately about 25 mg of the standard and transfer into a 25 ml volumetric flask. Add 15 ml of methanol to dissolve the sample, sonicate for 3 minutes. dilute to volume. mix.

Alternatively, weigh accurately about 25 mg of the standard (which contains known concentration of beta-boswellic acid) into 25 ml volumetric flask. Add 15 ml of methanol to dissolve the sample. sonicate for 3 minutes. dilute to volume. mix.

Chromatographic system:

The liquid chromatograph is equipped with 210nm and 256 nm UV detector and a 250 x 4.6 mm column that contains the packing C18 or ODS (Sigma/Aldrich column is used). The flow rate is 1.0 ml per min. The relative standard deviation for replicate injection of Standard preparation should not be more than 2%.

Procedure:

Separately inject equal volume (20ul) of the standard preparations and sample preparation into the chromatograph. record the responses for the peak of beta-boswellic acid and acetyl-beta-boswellic acid at 210nm and for the peaks of 11-keto-beta-boswellic acid and acetyl-11-ketoboswellic acid at 245 nm and calculate the percentage by weight of each boswellic acids as follows:

The following are the retention times of the four beta Boswellic acids:

1. Beta-boswellic acid.....17.4min
2. 3-acetyl beta-boswellic acid.....26.0min
3. 11-keto-beta-boswellic acid.....7.2min
4. 3-acetyl-11-keto-beta-boswellic acid.....10.4min

$$\frac{\text{Area of Sample} \times \text{Standard concentration in mg/ml} \times \text{Purity of the standard}}{\text{Area of Standard} \times \text{Sample concentration in mg/ml}}$$

Results of HPLC assay of pentacyclic triterpinic acids

Description	Old Plant Batch	RD/BS/21 New R&D Batch (1 kg)	New Trial Plant Batch (100 kg)
Beta-Boswellic acid	10.3 wt%	15 wt%	14 wt%
Acetyl-beta-boswellic acid	7.1 wt%	11 wt%	13.5 wt%
11-keto-boswellic acid	3.3 wt%	6.5 wt%	6.5 wt%
Acetyl-keto-beta-boswellic acid	3.4 wt%	7.6 wt%	7.5 wt%
TOTAL%	24.1 wt%	40.1 wt%	41.5 wt%

Wherein "Old" means the old process and "New" means the new process.

The "total organic acids" extract of the present invention can be obtained by a process comprising the following steps:

(1) providing a *Boswellia serrata* component:

(2) extracting the component with a C_1-C_6 alcohol. e.g. isopropyl alcohol. to obtain an alcohol extract:

(3) remove the C_1-C_6 alcohol from the alcohol extract to obtain a liquid:

(4) treat the liquid with an alkaline substance. such as an alkali. e.g. KOH. to obtain an alkaline liquid:

(5) wash the alkaline liquid with an organic solvent, e.g. ethyl acetate;

(6) remove the organic solvent to obtain an aqueous liquid; and thereafter

(7) treat the aqueous liquid with an acid, e.g. hydrochloric acid, to form the "total organic acids" extract as a precipitate.

Preferably, the *Boswellia serrata* component used is *Boswellia serrata* gum. The component in step (2) is preferably treated with hot isopropyl alcohol at a temperature of about 50-80°C, about 60-75°C, about 68-72°C or about 70°C. The treatment with KOH in step (4) preferably is carried out at pH>9.5. Step (7) is preferably conducted by treating the aqueous liquid with hydrochloric acid at about pH 3 to 4 to obtain a precipitate, which optionally can be washed with water and dried at a temperature less than about 50°C.

From the "total organic acids" extract obtained by the new process of the present invention, individual pure oswellic acids, i.e. compounds I, II, III or IV, can be obtained by chromatographic methods known in the prior art. The pure compound I, II, III and IV can also be obtained by synthetic processes known in the art. The individual pure oswellic acid can be mixed in any ratio to obtain desired mixtures.

The present invention includes compositions comprising the "total organic acids" extract obtained by the new process of the invention, any one of pure compound I, II, III or IV, or mixtures of two, three or all of compounds I-IV, mixed with a physiologically acceptable carrier or excipient.

The compositions of the present invention can comprise compound I : compound II : compound III : compound IV in any proportions. Preferably, the compositions comprise compound I : compound II : compound III : compound IV of 10-20 : 5-25 : 1-15 : 1-20 (or 15-20 : 5-25 : 1-15 : 1-20). More preferably, the compositions comprise compound I : compound II : compound III : compound IV of 12-17 : 7-18 : 3-10 : 2-15. Much preferred compositions of the present invention comprise compound I : compound II : compound III : compound IV of 14-16 : 8-17 : 4-9 : 3-10. Most preferred compositions of the present invention comprise compound I : compound II : compound III : compound IV of 15 : 10-15 : 5-8 : 4-8.

Another aspect of the present invention is a composition consisting essentially of, based on the total weight of the composition, β-boswellic acid of at least 12% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 1% by weight and acetyl-11-keto-β-boswellic acid of at least 1% by weight. This composition can contain other boswellic acids, e.g. 3a-hydroxy-urs-9,12-diene-24-oic acid or 2a,3a-dihydroxy-urs-12-ene-24-oic acid, each of which at a content of less than 1% by weight, based on the total weight of the composition. Preferably, the composition consists essentially of, based on the total weight of the composition, β-boswellic acid of at least 14% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 5% by weight and acetyl-11-keto-β-boswellic acid of at least 5% by weight. Also preferably, the composition consists essentially of, based on the total weight of the composition, β-boswellic acid of 12 to 35% by weight, acetyl-β-boswellic acid of 5 to 35% by weight, 11-keto-β-boswellic acid of 5 to 45% by weight and acetyl-11-keto-β-boswellic acid of 5 to 45% by weight. The composition, also preferably, consists essentially of, based on the total weight of the composition, β-boswellic acid of 12 to 30% by weight, acetyl-β-boswellic acid of 10 to 25% by weight, 11-keto-β-boswellic acid of 5 to 35% by weight and acetyl-11-keto-β-boswellic acid of 5 to 35% by weight. More preferably, the composition consists essentially of, based on the total weight of the composition, β-boswellic acid of 14 to 30% by weight, acetyl-β-boswellic acid of 10 to 20% by weight, 11-keto-β-boswellic acid of 5 to 25% by weight and acetyl-11-keto-β-boswellic acid of 5 to 25% by weight. Also more preferably, the composition consists essentially of, based on the total weight of the composition, β-boswellic acid of 14 to 35% by weight, acetyl-β-boswellic acid of 10 to 20% by weight, 11-keto-β-boswellic acid of 5 to 25% by weight and acetyl-11-keto-β-boswellic acid of 5 to 20% by weight. Also more preferably, the composition consists essentially of, based on the total weight of the composition, β-boswellic acid of 14 to 35% by weight, acetyl-β-boswellic acid of 10 to 20% by weight, 11-keto-β-boswellic acid of 5 to 20% by weight and acetyl-11-keto-β-boswellic acid of 5 to 25% by weight.

Another aspect of the present invention is a composition comprising three boswellic acids selected from the group consisting of β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid, wherein, based on the total weight of the composition, the amount of β-boswellic acid is at least 5% by weight, the amount of acetyl-β-boswellic acid of is least 5% by weight, the amount of 11-keto-β-boswellic acid is at least 5% by weight, and the amount of acetyl-11-keto-β-boswellic acid is at least 5% by weight. Preferably, in the composition, the amount of β-boswellic acid is 14 to 65% by weight, the amount of acetyl-β-boswellic acid is 5 to 65% by weight, the amount of 11-keto-β-boswellic acid is 5 to 60% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 5 to 60% by weight. Also preferably, in the composition, the amount of β-boswellic acid is 14 to 55% by weight, the amount of acetyl-β-boswellic acid is 10 to 55% by weight, the amount of 11-keto-β-boswellic acid is 5 to 50% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 5 to 50% by weight. Also preferably, in the composition, the amount of β-boswellic acid is 14 to 35% by weight, the amount of acetyl-β-boswellic acid is 10 to 35% by weight, the amount of 11-keto-β-boswellic acid is 5 to 40% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 5 to 40% by weight. Also preferably, in the composition, the β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid are derived from any natural source. Also preferably, in the composition, two of the three boswellic acids are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

Another aspect of the present invention is a composition comprising two boswellic acids selected from the group consisting of β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid, wherein, based on the total weight of the composition, the amount of β-boswellic acid is at least 5% by weight, the amount of acetyl-β-boswellic acid is least 5% by weight, the amount of 11-keto-β-boswellic acid is at least 5% by weight, and the amount of acetyl-11-keto-β-boswellic acid is at least 5% by weight. Preferably, in the composition, the amount of β-boswellic acid is 5 to 95% by weight, the amount of acetyl-β-boswellic acid is 5 to 95% by weight, the amount of 11-keto-β-boswellic

acid is 5 to 95% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 5 to 95% by weight. Preferably, in the composition, the amount of β-boswellic acid is 30 to 70% by weight, the amount of acetyl-β-boswellic acid is 30 to 70% by weight, the amount of 11-keto-β-boswellic acid is 30 to 70% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 30 to 70% by weight. Also preferably, in the composition, the amount of β-boswellic acid is 40 to 60% by weight, the amount of acetyl-β-boswellic acid is 40 to 60% by weight, the amount of 11-keto-β-boswellic acid is 40 to 60% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 40 to 60% by weight. Also preferably, in the composition, the two boswellic acids are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

Within the scope of the present invention is a composition comprising boswellic acids, wherein the boswellic acids consist of three substances selected from the group consisting of β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid, wherein, based on the total weight of the composition, the amount of β-boswellic acid is at least 5% by weight, the amount of acetyl-β-boswellic acid is least 5% by weight, the amount of 11-keto-β-boswellic acid is at least 5% by weight, and the amount of acetyl-11-keto-β-boswellic acid is at least 5% by weight. Preferably, in the composition, the amount of β-boswellic acid is 5 to 65% by weight, the amount of acetyl-β-boswellic acid is 5 to 65% by weight, the amount of 11-keto-β-boswellic acid is 5 to 65% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 5 to 65% by weight. Also preferably, in the composition, the amount of β-boswellic acid is 15 to 55% by weight, the amount of acetyl-β-boswellic acid is 15 to 55% by weight, the amount of 11-keto-β-boswellic acid is 15 to 55% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 15 to 55% by weight. Also preferably, in the composition, the amount of β-boswellic acid is 20 to 40% by weight, the amount of acetyl-β-boswellic acid is 20 to 40% by weight, the amount of 11-keto-β-boswellic acid is 20 to 40% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 20 to 40% by weight. Also preferably, in the composition, two of the three substances are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

Another aspect of the present invention is a composition comprising boswellic acids, wherein the boswellic acids consist of two substances selected from the group consisting of β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid, wherein, based on the total weight of the boswellic acids, the amount of β-boswellic acid is at least 5% by weight, the amount of acetyl-β-boswellic acid of is least 5% by weight, the amount of 11-keto-β-boswellic acid is at least 5% by weight, and the amount of acetyl-11-keto-β-boswellic acid is at least 5% by weight. Preferably, in the composition, the amount of β-boswellic acid is 10 to 90% by weight, the amount of acetyl-β-boswellic acid is 10 to 90% by weight, the amount of 11-keto-β-boswellic acid is 10 to 90% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 10 to 90% by weight. Also preferably, in the composition, the amount of β-boswellic acid is 20 to 80% by weight, the amount of acetyl-β-boswellic acid is 20 to 80% by weight, the amount of 11-keto-β-boswellic acid is 20 to 80% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 20 to 80% by weight. Also preferably, in the composition, the amount of β-boswellic acid is 30 to 70% by weight, the amount of acetyl-β-boswellic acid is 30 to 70% by weight, the amount of 11-keto-β-boswellic acid is 30 to 70% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 30 to 70% by weight. Also preferably, in the composition, the amount of β-boswellic acid is 40 to 60% by weight, the amount of acetyl-β-boswellic acid is 40 to 60% by weight, the amount of 11-keto-β-boswellic acid is 40 to 60% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 40 to 60% by weight. Also preferably, in the composition, the two substances are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

Another embodiment of the present invention is a method for inhibition of DNA, RNA and/or protein synthesis in a human or animal in need of the inhibition, wherein the method comprises a step of administering a DNA, RNA and/or protein synthesis inhibition effective amount of a composition to said human or animal, wherein the composition comprises β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid. Preferably, the composition comprises β-boswellic acid of at least 12% by weight, acetyl-β-

boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 1% by weight and acetyl-11-keto-β-boswellic acid of at least 1% by weight. More preferably, the composition comprises β-boswellic acid of 12 to 35% by weight, acetyl-β-boswellic acid of 5 to 35% by weight, 11-keto-β-boswellic acid of 5 to 45% by weight and acetyl-11-keto-β-boswellic acid of 5 to 45% by weight.

Another embodiment of the present invention is a method for irreversible inhibition of DNA synthesis in a human or animal in need of the inhibition, comprising a step of administering an irreversible DNA inhibition effective amount of a composition to said human or animal, wherein the composition comprises β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid. Preferably, for used in the method, the composition comprises β-boswellic acid of at least 12% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 1% by weight and acetyl-11-keto-β-boswellic acid of at least 1% by weight. For used in the method, the composition more preferably comprises β-boswellic acid of 12 to 35% by weight, acetyl-β-boswellic acid of 5 to 35% by weight, 11-keto-β-boswellic acid of 5 to 45% by weight and acetyl-11-keto-β-boswellic acid of 5 to 45% by weight.

Within the scope of the present invention is a method for the prevention or treatment of a lymphoproliferative disease in a human or animal in need of the prevention or treatment, wherein the method comprises a step of administering a lymphoproliferative disease prevention or treatment effective amount of a composition to said human or animal, wherein the composition comprises β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid. Preferably, for used in the method, the composition comprises β-boswellic acid of at least 12% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 1% by weight and acetyl-11-keto-β-boswellic acid of at least 1% by weight. More preferably, for used in the method, the composition comprises β-boswellic acid of 12 to 35% by weight, acetyl-β-boswellic acid of 5 to 35% by weight, 11-keto-β-boswellic acid of 5 to 45% by weight and acetyl-11-keto-β-boswellic acid of 5 to 45% by weight.

Another aspect of the present invention is a method for the prevention or treatment of an autoimmune disease in a human or animal in need of the prevention or treatment, wherein the method comprises a step of administering an autoimmune disease prevention or treatment effective amount of a composition to said human or animal, wherein the composition comprises β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid. Preferably, for used in the method, the composition comprises β-boswellic acid of at least 12% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 1% by weight and acetyl-11-keto-β-boswellic acid of at least 1% by weight. More preferably, for used in the method, the composition comprises β-boswellic acid of 12 to 35% by weight, acetyl-β-boswellic acid of 5 to 35% by weight, 11-keto-β-boswellic acid of 5 to 45% by weight and acetyl-11-keto-β-boswellic acid of 5 to 45% by weight.

Another aspect of the present invention is a method of inhibiting the synthesis of DNA, RNA and/or protein in a human or animal in need of the inhibition, comprising administering a DNA, RNA and/or protein synthesis inhibition effective amount of β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid or acetyl-11-keto-β-boswellic acid.

Another aspect of the present invention is a method for irreversibly inhibiting the synthesis of DNA in a human or animal in need of the inhibition, comprising administering a DNA synthesis reversible inhibition effective amount of β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid or acetyl-11-keto-β-boswellic acid.

Another aspect of the present invention is a method for preventing or treating a lymphoproliferative disease in a human or animal in need of the prevention or treatment, comprising administering a lymphoproliferative disease preventing or treating effective amount of β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid or acetyl-11-keto-β-boswellic acid.

Another aspect of the present invention is a method for preventing or treating an autoimmune disease in a human or animal in need of the prevention or treatment, comprising administering an autoimmune disease preventing or treating effective

amount of β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid or acetyl-11-keto-β-boswellic acid.

Also within the scope of the present invention are methods of using the compositions or boswellic acid(s), individually or mixtures thereof, of the present invention to make a medication for inhibiting the synthesis of DNA, RNA and/or protein, for irreversibly inhibiting the synthesis of DNA, for preventing or treating a lymphoproliferative or autoimmune disease.

Also preferably, in the compositions of the present invention, the β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid are derived from any natural source.

Within the scope of the present invention is a second new extraction process to obtain boswellic acids from *Boswellia serrata*. The second new extraction process of obtaining boswellic acids comprises the following steps:

(a) providing a *Boswellia serrata* component;

(b) extracting said *Boswellia serrata* component with carbon dioxide to obtain a fluid extract; and

(c) removing carbon dioxide from the fluid extract to obtain the boswellic acids.

In the second new extraction process, the *Boswellia serrata* component preferably is a gum or degummed resin from *Boswellia serrata*. The extracting step in the second new extraction process can be performed with subcritical extraction or supercritical extraction using liquid carbon dioxide. After the removal of carbon dioxide from the fluid extract, the so obtained boswellic acids can be, if necessary, subjected to further separation or purification, such as chromatography or selective precipitation in appropriate organic solvents.

Carbon dioxide may be used as an extracting solvent in either of two forms - subcritical and supercritical. Carbon dioxide has a critical temperature of 31.2°C and a critical pressure of 73.8 bars (1070 psi). The subcritical extraction is performed in the liquid state at a pressure in the range of 300 to 700 psi (20 to 48 bars) and a temperature or temperatures ranging from 0° to 31°C. The supercritical

extraction is performed in the fluid gas state at a temperature or temperatures above the critical temperature (31.2°C or 89°F) and a pressure in the range of 2000 to 4000 psi (138 to 275 bars). The second new extraction process using supercritical extraction gives a higher yield in a shorter time.

For subcritical extractions, high pressure batch or continuous extraction systems may be used. For supercritical extractions, suitable equipment includes packed or plate columns, towers featuring perforated plates or baffle structures, mixer-settler type equipment equipped with internal mixing elements, and extraction devices utilizing centrifugal force can be used.

As a working example of the second new extraction process, a batch extraction device was used, wherein the material was extracted with liquid carbon dioxide. Drums containing 80 kg of degummed resin from *Boswellia serrata* were charged into a suitable extraction chamber and contacted with liquid carbon dioxide for 2 hours. Each 80 kg charge yielded at least 18 kg of an enriched pasty material containing boswellic acids and other organic acids.

Also within the scope of the present invention is an extract obtained from *Boswellia serrata* obtained with one of the new extraction processes of the present invention. For instance, a total organic acids extract from *Boswellia serrata* can be obtained with the first or second new extraction process of the present invention.

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Claims

1. A composition consisting essentially of, based on the total weight of the composition, β-boswellic acid of at least 12% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 1% by weight and acetyl-11-keto-β-boswellic acid of at least 1% by weight.

2. The composition of claim 1 consisting essentially of, based on the total weight of the composition, β-boswellic acid of at least 14% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 5% by weight and acetyl-11-keto-β-boswellic acid of at least 5% by weight.

3. The composition of claim 1 consisting essentially of, based on the total weight of the composition, β-boswellic acid of 12 to 35% by weight, acetyl-β-boswellic acid of 5 to 35% by weight, 11-keto-β-boswellic acid of 5 to 45% by weight and acetyl-11-keto-β-boswellic acid of 5 to 45% by weight.

4. The composition of claim 3 consisting essentially of, based on the total weight of the composition, β-boswellic acid of 12 to 30% by weight, acetyl-β-boswellic acid of 10 to 25% by weight, 11-keto-β-boswellic acid of 5 to 35% by weight and acetyl-11-keto-β-boswellic acid of 5 to 35% by weight.

5. The composition of claim 4 consisting essentially of, based on the total weight of the composition, β-boswellic acid of 14 to 30% by weight, acetyl-β-boswellic acid of 10 to 20% by weight, 11-keto-β-boswellic acid of 5 to 25% by weight and acetyl-11-keto-β-boswellic acid of 5 to 25% by weight.

6. The composition of claim 3 consisting essentially of, based on the total weight of the composition, β-boswellic acid of 14 to 35% by weight, acetyl-β-boswellic acid of 10 to 20% by weight, 11-keto-β-boswellic acid of 5 to 25% by weight and acetyl-11-keto-β-boswellic acid of 5 to 20% by weight.

7. The composition of claim 3 consisting essentially of, based on the total weight of the composition, β-boswellic acid of 14 to 35% by weight, acetyl-β-boswellic acid of 10 to 20% by weight, 11-keto-β-boswellic acid of 5 to 20% by weight and acetyl-11-keto-β-boswellic acid of 5 to 25% by weight.

8. The composition of claim 1, wherein the β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid are derived from any natural source.

9. A composition comprising three boswellic acids selected from the group consisting of β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid, wherein, based on the total weight of the composition, the amount of β-boswellic acid is at least 5% by weight, the amount of acetyl-β-boswellic acid of is least 5% by weight, the amount of 11-keto-β-boswellic acid is at least 5% by weight, and the amount of acetyl-11-keto-β-boswellic acid is at least 5% by weight.

10. The composition of claim 9, wherein the amount of β-boswellic acid is 14 to 65% by weight, the amount of acetyl-β-boswellic acid is 5 to 65% by weight, the amount of 11-keto-β-boswellic acid is 5 to 60% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 5 to 60% by weight.

11. The composition of claim 10, wherein the amount of β-boswellic acid is 14 to 55% by weight, the amount of acetyl-β-boswellic acid is 10 to 55% by weight, the amount of 11-keto-β-boswellic acid is 5 to 50% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 5 to 50% by weight.

12. The composition of claim 11, wherein the amount of β-boswellic acid is 14 to 35% by weight, the amount of acetyl-β-boswellic acid is 10 to 35% by weight, the amount of 11-keto-β-boswellic acid is 5 to 40% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 5 to 40% by weight.

13. The composition of claim 9, wherein the β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid are derived from any natural source.

14. A composition comprising two boswellic acids selected from the group consisting of β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid, wherein, based on the total weight of the composition, the amount of β-boswellic acid is at least 5% by weight, the amount of acetyl-β-boswellic acid is least 5% by weight, the amount of 11-keto-β-boswellic

acid is at least 5% by weight, and the amount of acetyl-11-keto-β-boswellic acid is at least 5% by weight.

15. The composition of claim 14, wherein the amount of β-boswellic acid is 5 to 95% by weight, the amount of acetyl-β-boswellic acid is 5 to 95% by weight, the amount of 11-keto-β-boswellic acid is 5 to 95% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 5 to 95% by weight.

16. The composition of claim 15, wherein the amount of β-boswellic acid is 30 to 70% by weight, the amount of acetyl-β-boswellic acid is 30 to 70% by weight, the amount of 11-keto-β-boswellic acid is 30 to 70% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 30 to 70% by weight.

17. The composition of claim 16, wherein the amount of β-boswellic acid is 40 to 60% by weight, the amount of acetyl-β-boswellic acid is 40 to 60% by weight, the amount of 11-keto-β-boswellic acid is 40 to 60% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 40 to 60% by weight.

18. The composition of claim 14, wherein the β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid are derived from any natural source.

19. A composition comprising boswellic acids, wherein the boswellic acids consist of three substances selected from the group consisting of β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid, wherein, based on the total weight of the composition, the amount of β-boswellic acid is at least 5% by weight, the amount of acetyl-β-boswellic acid of is least 5% by weight, the amount of 11-keto-β-boswellic acid is at least 5% by weight, and the amount of acetyl-11-keto-β-boswellic acid is at least 5% by weight.

20. The composition of claim 19, wherein the amount of β-boswellic acid is 5 to 65% by weight, the amount of acetyl-β-boswellic acid is 5 to 65% by weight, the amount of 11-keto-β-boswellic acid is 5 to 65% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 5 to 65% by weight.

21. The composition of claim 20, wherein the amount of β-boswellic acid is 15 to 55% by weight, the amount of acetyl-β-boswellic acid is 15 to 55% by

weight, the amount of 11-keto-β-boswellic acid is 15 to 55% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 15 to 55% by weight.

22. The composition of claim 21, wherein the amount of β-boswellic acid is 20 to 40% by weight, the amount of acetyl-β-boswellic acid is 20 to 40% by weight, the amount of 11-keto-β-boswellic acid is 20 to 40% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 20 to 40% by weight.

23. The composition of claim 19, wherein the β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid are derived from any natural source.

24. A composition comprising boswellic acids, wherein the boswellic acids consist of two substances selected from the group consisting of β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid, wherein, based on the total weight of the boswellic acids, the amount of β-boswellic acid is at least 5% by weight, the amount of acetyl-β-boswellic acid of is least 5% by weight, the amount of 11-keto-β-boswellic acid is at least 5% by weight, and the amount of acetyl-11-keto-β-boswellic acid is at least 5% by weight.

25. The composition of claim 24, wherein the amount of β-boswellic acid is 10 to 90% by weight, the amount of acetyl-β-boswellic acid is 10 to 90% by weight, the amount of 11-keto-β-boswellic acid is 10 to 90% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 10 to 90% by weight.

26. The composition of claim 25, wherein the amount of β-boswellic acid is 20 to 80% by weight, the amount of acetyl-β-boswellic acid is 20 to 80% by weight, the amount of 11-keto-β-boswellic acid is 20 to 80% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 20 to 80% by weight.

27. The composition of claim 26, wherein the amount of β-boswellic acid is 30 to 70% by weight, the amount of acetyl-β-boswellic acid is 30 to 70% by weight, the amount of 11-keto-β-boswellic acid is 30 to 70% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 30 to 70% by weight.

28. The composition of claim 27, wherein the amount of β-boswellic acid is 40 to 60% by weight, the amount of acetyl-β-boswellic acid is 40 to 60% by

weight, the amount of 11-keto-β-boswellic acid is 40 to 60% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 40 to 60% by weight.

29. The composition of claim 9, wherein two of the three boswellic acids are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

30. The composition of claim 9, wherein two of the three boswellic acids are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

31. The composition of claim 11, wherein two of the three boswellic acids are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

32. The composition of claim 12, wherein two of the three boswellic acids are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

33. The composition of claim 14, wherein the two boswellic acids are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

34. The composition of claim 15, wherein the two boswellic acids are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

35. The composition of claim 16, wherein the two boswellic acids are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

36. The composition of claim 17, wherein the two boswellic acids are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

37. The composition of claim 19, wherein two of the three substances are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

38. The composition of claim 20, wherein two of the three substances are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

39. The composition of claim 21, wherein two of the three substances are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

40. The composition of claim 22, wherein two of the three substances are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

41. The composition of claim 24, wherein the two substances are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

42. The composition of claim 25, wherein the two substances are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

43. The composition of claim 26, wherein the two substances are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

44. The composition of claim 27, wherein the two substances are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

45. A method for inhibition of DNA, RNA and/or protein synthesis in a human or animal in need of the inhibition, comprising a step of administering a DNA, RNA and/or protein synthesis inhibition effective amount of a composition to said human or animal, wherein the composition comprises β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

46. The method of claim 45, wherein the composition comprises β-boswellic acid of at least 12% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 1% by weight and acetyl-11-keto-β-boswellic acid of at least 1% by weight.

47. The method of claim 46, wherein the composition comprises β-boswellic acid of 12 to 35% by weight, acetyl-β-boswellic acid of 5 to 35% by weight, 11-keto-β-boswellic acid of 5 to 45% by weight and acetyl-11-keto-β-boswellic acid of 5 to 45% by weight.

48. A method for irreversible inhibition of DNA synthesis in a human or animal in need of the inhibition, comprising a step of administering a DNA inhibition effective amount of a composition to said human or animal, wherein the composition comprises β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

49. The method of claim 48, wherein the composition comprises β-boswellic acid of at least 12% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 1% by weight and acetyl-11-keto-β-boswellic acid of at least 1% by weight.

50. The method of claim 49, wherein the composition comprises β-boswellic acid of 12 to 35% by weight, acetyl-β-boswellic acid of 5 to 35% by weight, 11-keto-β-boswellic acid of 5 to 45% by weight and acetyl-11-keto-β-boswellic acid of 5 to 45% by weight.

51. A method for the prevention of a lymphoproliferative disease in a human or animal in need of the prevention, comprising a step of administering a lymphoproliferative disease prevention effective amount of a composition to said human or animal, wherein the composition comprises β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

52. The method of claim 51, wherein the composition comprises β-boswellic acid of at least 12% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 1% by weight and acetyl-11-keto-β-boswellic acid of at least 1% by weight.

53. The method of claim 52, wherein the composition comprises β-boswellic acid of 12 to 35% by weight, acetyl-β-boswellic acid of 5 to 35% by weight, 11-keto-β-boswellic acid of 5 to 45% by weight and acetyl-11-keto-β-boswellic acid of 5 to 45% by weight.

54. The method of claim 51, wherein the lymphoproliferative disease is leukemia or lymphoma.

55. A method for the treatment of a lymphoproliferative disease in a human or animal in need of the treatment, comprising a step of administering a lymphoproliferative disease treatment effective amount of a composition to said human or animal, wherein the composition comprises β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

56. The method of claim 55, wherein the composition comprises β-boswellic acid of at least 12% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 1% by weight and acetyl-11-keto-β-boswellic acid of at least 1% by weight.

57. The method of claim 56, wherein the composition comprises β-boswellic acid of 12 to 35% by weight, acetyl-β-boswellic acid of 5 to 35% by weight, 11-keto-β-boswellic acid of 5 to 45% by weight and acetyl-11-keto-β-boswellic acid of 5 to 45% by weight.

58. The method of claim 55, wherein the lymphoproliferative disease is leukemia or lymphoma.

59. A method for the prevention of an autoimmune disease in a human or animal in need of the prevention, comprising a step of administering an autoimmune disease prevention effective amount of a composition to said human or animal, wherein the composition comprises β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

60. The method of claim 59, wherein the composition comprises β-boswellic acid of at least 12% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 1% by weight and acetyl-11-keto-β-boswellic acid of at least 1% by weight.

61. The method of claim 60, wherein the composition comprises β-boswellic acid of 12 to 35% by weight, acetyl-β-boswellic acid of 5 to 35% by weight, 11-keto-β-boswellic acid of 5 to 45% by weight and acetyl-11-keto-β-boswellic acid of 5 to 45% by weight.

62. The method of claim 59, wherein the autoimmune disease is psoriasis, sarcoidosis, systemic lupus erythematosis, Grave's disease, Hashimoto's thyroiditis, silent thyroiditis, Crohn's disease, Goodpasture syndrome, insulin-dependent diabetes mellitus, insulin-resistant diabetes mellitus, myasthenia gravis, Addison's disease, idiopathic hypoparathyroidism, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, rheumatoid arthritis or scleroderma.

63. A method for the treatment of an autoimmune disease in a human or animal in need of the treatment, comprising a step of administering an autoimmune disease treatment effective amount of a composition to said human or animal, wherein the composition comprises β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

64. The method of claim 63, wherein the composition comprises β-boswellic acid of at least 12% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 1% by weight and acetyl-11-keto-β-boswellic acid of at least 1% by weight.

65. The method of claim 64, wherein the composition comprises β-boswellic acid of 12 to 35% by weight, acetyl-β-boswellic acid of 5 to 35% by

weight. 11-keto-β-boswellic acid of 5 to 45% by weight and acetyl-11-keto-β-boswellic acid of 5 to 45% by weight.

66. The method of claim 63, wherein the autoimmune disease is psoriasis, sarcoidosis, systemic lupus erythematosis, Grave's disease, Hashimoto's thyroiditis, silent thyroiditis, Crohn's disease, Goodpasture syndrome, insulin-dependent diabetes mellitus, insulin-resistant diabetes mellitus, myasthenia gravis, Addison's disease, idiopathic hypoparathyroidism, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, rheumatoid arthritis or scleroderma.

67. A process of obtaining a total organic acids extract from *Boswellia serrata*, wherein the total organic acids extract comprises boswellic acids, said process comprising the following steps:

(1) providing a *Boswellia serrata* component;

(2) extracting the component with a C_1-C_6 alcohol to obtain an alcohol extract;

(3) removing the C_1-C_6 alcohol from the alcohol extract to obtain a liquid;

(4) treating the liquid with an alkaline substance to obtain an alkaline liquid;

(5) washing the alkaline liquid with an organic solvent;

(6) removing the organic solvent to obtain an aqueous liquid; and thereafter

(7) treating the aqueous liquid with an acid to obtain the total organic acids extract as a precipitate.

68. The process of claim 67, wherein the *Boswellia serrata* component is the gum from *Boswellia serrata*.

69. The process of claim 67, wherein the C_1-C_6 alcohol in step (2) is isopropyl alcohol.

70. The process of claim 67, wherein said alkaline substance is KOH and said liquid in step (4) is treated with KOH at pH>9.5.

71. The process of claim 67, wherein said aqueous liquid in step (7) is treated with hydrochloric acid at about pH 3 to 4 to obtain the precipitate.

72. The process of claim 67, wherein the precipitate is washed with water and dried at a temperature less than about 50°C.

73. The process of claim 67, wherein the organic solvent is ethyl acetate.

74. A total organic acids extract from *Boswellia serrata* obtained by the process of claim 67.

75. A process of obtaining boswellic acids comprising the following steps:

(a) providing a *Boswellia serrata* component;

(b) extracting said *Boswellia serrata* component with carbon dioxide to obtain a fluid extract; and

(c) removing carbon dioxide from the fluid extract to obtain the boswellic acids.

76. The process of claim 75, wherein the *Boswellia serrata* component is a gum from *Boswellia serrata*.

77. The process of claim 75, wherein the extracting in step (b) is performed with subcritical extraction.

78. The process of claim 75, wherein the extracting in step (b) is performed with supercritical extraction.

79. A method for the treatment of a tumor in a human or animal in need of the treatment by administering a tumor treating effective amount of a composition to said human or animal, wherein the composition comprises β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

80. The method of claim 79, wherein the composition comprises β-boswellic acid of at least 12% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 1% by weight and acetyl-11-keto-β-boswellic acid of at least 1% by weight.

81. The method of claim 80, wherein the composition comprises β-boswellic acid of 12 to 35% by weight, acetyl-β-boswellic acid of 5 to 35% by weight, 11-keto-β-boswellic acid of 5 to 45% by weight and acetyl-11-keto-β-boswellic acid of 5 to 45% by weight.

82. A method of inhibiting the synthesis of DNA, RNA and/or protein in a human or animal in need of the inhibition, comprising administering a DNA, RNA and/or protein synthesis inhibition effective amount of β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid or acetyl-11-keto-β-boswellic acid.

83. A method for irreversibly inhibiting the synthesis of DNA in a human or animal in need of the inhibition, comprising administering a DNA synthesis inhibition effective amount of β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid or acetyl-11-keto-β-boswellic acid.

84. A method for preventing or treating a lymphoproliferative disease in a human or animal in need of the prevention or treatment, comprising administering a lymphoproliferative disease preventing or treating effective amount of β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid or acetyl-11-keto-β-boswellic acid.

85. A method for preventing or treating an autoimmune disease in a human or animal in need of the prevention or treatment, comprising administering an autoimmune disease preventing or treating effective amount of β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid or acetyl-11-keto-β-boswellic acid.

AMENDED CLAIMS
[received by the International Bureau on 15 November 2000 (15.11.00);
original claims 1-85 replaced by new claims 86-162 (13 pages)]

86. A composition consisting essentially of, based on the total weight of the composition, β-boswellic acid of at least 12% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 15% by weight and acetyl-11-keto-β-boswellic acid of at least 14% by weight.

87. The composition of claim 86 consisting essentially of, based on the total weight of the composition, β-boswellic acid of at least 14% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 55% by weight and acetyl-11-keto-β-boswellic acid of at least 14% by weight.

88. The composition of claim 86 consisting essentially of, based on the total weight of the composition, β-boswellic acid of 12 to 35% by weight, acetyl-β-boswellic acid of 5 to 35% by weight, 11-keto-β-boswellic acid of at least 15% by weight and acetyl-11-keto-β-boswellic acid of at least 14% by weight.

89. The composition of claim 88 consisting essentially of, based on the total weight of the composition, β-boswellic acid of 12 to 30% by weight, acetyl-β-boswellic acid of 10 to 25% by weight, 11-keto-β-boswellic acid of at least 15% by weight and acetyl-11-keto-β-boswellic acid of at least 14% by weight.

90. The composition of claim 89 consisting essentially of, based on the total weight of the composition, β-boswellic acid of 14 to 30% by weight, acetyl-β-boswellic acid of 10 to 20% by weight, 11-keto-β-boswellic acid of at least 15% by weight and acetyl-11-keto-β-boswellic acid of at least 14% by weight.

91. The composition of claim 88 consisting essentially of, based on the total weight of the composition, β-boswellic acid of 14 to 35% by weight, acetyl-β-boswellic acid of 10 to 20%

by weight, 11-keto-β-boswellic acid of at least 15% by weight and acetyl-11-keto-β-boswellic acid of at least 14% by weight.

92. The composition of claim 88 consisting essentially of, based on the total weight of the composition, β-boswellic acid of 14 to 35% by weight, acetyl-β-boswellic acid of 10 to 20% by weight, 11-keto-β-boswellic acid of at least 15% by weight and acetyl-11-keto-β-boswellic acid of at least 14% by weight.

93. The composition of claim 86, wherein the β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid are derived from any natural source.

94. A composition comprising three boswellic acids selected from the group consisting of β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid, wherein, based on the total weight of the composition, the amount of β-boswellic acid is at least 5% by weight, the amount of acetyl-β-boswellic acid of is least 5% by weight, the amount of 11-keto-β-boswellic acid is at least 15% by weight, and the amount of acetyl-11-keto-β-boswellic acid is at least 14% by weight.

95. The composition of claim 94, wherein the amount of β-boswellic acid is 14 to 65% by weight, the amount of acetyl-β-boswellic acid is 5 to 65% by weight, the amount of 11-keto-β-boswellic acid is 15 to 60% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 14 to 60% by weight.

96. The composition of claim 95, wherein the amount of β-boswellic acid is 14 to 55% by weight, the amount of acetyl-β-boswellic acid is 10 to 55% by weight, the amount of 11-keto-β-boswellic acid is 15 to 50% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 14 to 50% by weight.

97. The composition of claim 96, wherein the amount of β-boswellic acid is 14 to 35% by weight, the amount of acetyl-β-boswellic acid is 10 to 35% by weight, the amount of 11-keto-β-boswellic acid is 15 to 40% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 14 to 40% by weight.

98. The composition of claim 94, wherein the β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid are derived from any natural source.

99. A composition comprising two boswellic acids selected from the group consisting of β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid, wherein, based on the total weight of the composition, the amount of β-boswellic acid is 1 to 34% or at least 56% by weight, the amount of acetyl-β-boswellic acid is 1 to 24% or at least 46% by weight, the amount of 11-keto-β-boswellic acid is at least 15% by weight, and the amount of acetyl-11-keto-β-boswellic acid is at least 14% by weight.

100. The composition of claim 99, wherein the amount of β-boswellic acid is 1 to 34% or 56 to 95% by weight, the amount of acetyl-β-boswellic acid is 1 to 24% or 46 to 95% by weight, the amount of 11-keto-β-boswellic acid is 15 to 95% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 14 to 95% by weight.

101. The composition of claim 100, wherein the amount of β-boswellic acid is 1 to 34% or 56 to 70% by weight, the amount of acetyl-β-boswellic acid is 1 to 24% or 46 to 70% by weight, the amount of 11-keto-β-boswellic acid is 30 to 70% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 30 to 70% by weight.

102. The composition of claim 101, wherein the amount of β-boswellic acid is 1 to 34% or 40 to 60% by weight, the amount of acetyl-β-boswellic acid is 1 to 24% or 40 to 60% by weight, the amount of 11-keto-β-boswellic acid is 40 to 60% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 40 to 60% by weight.

103. The composition of claim 99, wherein the β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid are derived from any natural source.

104. A composition comprising boswellic acids, wherein the boswellic acids consist of three substances selected from the group consisting of β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid, wherein, based on the total weight of the composition, the amount of β-boswellic acid is at least 5% by weight, the amount of acetyl-β-boswellic acid of is least 5% by weight, the amount of 11-keto-β-boswellic acid is at least 15% by weight, and the amount of acetyl-11-keto-β-boswellic acid is at least 14% by weight.

105. The composition of claim 104, wherein the amount of β-boswellic acid is 5 to 65% by weight, the amount of acetyl-β-boswellic acid is 5 to 65% by weight, the amount of 11-keto-β-boswellic acid is 15 to 65% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 14 to 65% by weight.

106. The composition of claim 105, wherein the amount of β-boswellic acid is 15 to 55% by weight, the amount of acetyl-β-boswellic acid is 15 to 55% by weight, the amount of 11-keto-β-boswellic acid is 15 to 55% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 15 to 55% by weight.

107. The composition of claim 106, wherein the amount of β-boswellic acid is 20 to 40% by weight, the amount of acetyl-β-boswellic acid is 20 to 40% by weight, the amount of 11-keto-β-boswellic acid is 20 to 40% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 20 to 40% by weight.

108. The composition of claim 104, wherein the β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid are derived from any natural source.

109. A composition comprising boswellic acids, wherein the boswellic acids consist of two substances selected from the group consisting of β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid, wherein, based on the total weight of the boswellic acids, the amount of β-boswellic acid is 1 to 34% or at least 56% by weight, the amount of acetyl-β-boswellic acid of is 1 to 24% or at least 46% by weight, the amount of 11-keto-β-boswellic acid is at least 15% by weight, and the amount of acetyl-11-keto-β-boswellic acid is at least 14% by weight.

110. The composition of claim 109, wherein the amount of β-boswellic acid is 1 to 34% or 56 to 90% by weight, the amount of acetyl-β-boswellic acid is 1 to 24% or 46 to 90% by weight, the amount of 11-keto-β-boswellic acid is 15 to 90% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 14 to 90% by weight.

111. The composition of claim 110, wherein the amount of β-boswellic acid is 1 to 34% or 56 to 80% by weight, the amount of acetyl-β-boswellic acid is 1 to 24% or 46 to 80% by weight, the amount of 11-keto-β-boswellic acid is 20 to 80% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 20 to 80% by weight.

112. The composition of claim 111, wherein the amount of β-boswellic acid is 1 to 34% or 56 to 70% by weight, the amount of acetyl-β-boswellic acid is 1 to 24% or 46 to 70% by weight, the amount of 11-keto-β-boswellic acid is 30 to 70% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 30 to 70% by weight.

113. The composition of claim 112, wherein the amount of β-boswellic acid is 1 to 34% or 56 to 60% by weight, the amount of acetyl-β-boswellic acid is 1 to 24% or 46 to 60% by weight, the amount of 11-keto-β-boswellic acid is 40 to 60% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 40 to 60% by weight.

114. The composition of claim 94, wherein two of the three boswellic acids are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

115. The composition of claim 94, wherein two of the three boswellic acids are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

116. The composition of claim 96, wherein two of the three boswellic acids are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

117. The composition of claim 97, wherein two of the three boswellic acids are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

118. The composition of claim 99, wherein the two boswellic acids are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

119. The composition of claim 100, wherein the two boswellic acids are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

120. The composition of claim 101, wherein the two boswellic acids are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

121. The composition of claim 102, wherein the two boswellic acids are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

122. The composition of claim 104, wherein two of the three substances are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

123. The composition of claim 105, wherein two of the three substances are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

124. The composition of claim 106, wherein two of the three substances are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

125. The composition of claim 107, wherein two of the three substances are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

126. The composition of claim 109, wherein the two substances are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

127. The composition of claim 110, wherein the two substances are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

128. The composition of claim 111, wherein the two substances are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

129. The composition of claim 112, wherein the two substances are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

130. A method for inhibition of DNA, RNA and/or protein synthesis in a human or animal in need of the inhibition, comprising a step of administering a DNA, RNA and/or protein synthesis inhibition effective amount of a composition to said human or animal, wherein the composition comprises β-boswellic acid of at least 5% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 15% by weight and acetyl-11-keto-β-boswellic acid of at least 14% be weight.

131. The method of claim 130, wherein the composition comprises β-boswellic acid of at least 12% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 15% by weight and acetyl-11-keto-β-boswellic acid of at least 14% by weight.

132. The method of claim 131, wherein the composition comprises β-boswellic acid of 12 to 35% by weight, acetyl-β-boswellic acid of 5 to 35% by weight, 11-keto-β-boswellic acid of 15 to 45% by weight and acetyl-11-keto-β-boswellic acid of 14 to 45% by weight.

133. A method for irreversible inhibition of DNA synthesis in a human or animal in need of the inhibition, comprising a step of administering a DNA inhibition effective amount of a composition to said human or animal, wherein the composition comprises β-boswellic acid of at least 5% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 15% be weight and acetyl-11-keto-β-boswellic acid of at least 14% be weight.

134. The method of claim 133, wherein the composition comprises β-boswellic acid of at least 12% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 15% by weight and acetyl-11-keto-β-boswellic acid of at least 14% by weight.

135. The method of claim 134, wherein the composition comprises β-boswellic acid of 12 to 35% by weight, acetyl-β-boswellic acid of 5 to 35% by weight, 11-keto-β-boswellic acid of 15 to 45% by weight and acetyl-11-keto-β-boswellic acid of 14 to 45% by weight.

136. A method for the prevention of a lymphoproliferative disease in a human or animal in need of the prevention, comprising a step of administering a lymphoproliferative disease prevention effective amount of a composition to said human or animal, wherein the composition comprises β-boswellic acid of at least 5% be weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 15% be weight and acetyl-11-keto-β-boswellic acid of at least 14% by weight.

137. The method of claim 136, wherein the composition comprises β-boswellic acid of at least 12% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 15% by weight and acetyl-11-keto-β-boswellic acid of at least 14% by weight.

138. The method of claim 137, wherein the composition comprises β-boswellic acid of 12 to 35% by weight, acetyl-β-boswellic acid of 5 to 35% by weight, 11-keto-β-boswellic acid of 15 to 45% by weight and acetyl-11-keto-β-boswellic acid of 14 to 45% by weight.

139. The method of claim 136, wherein the lymphoproliferative disease is leukemia or lymphoma.

140. A method for the treatment of a lymphoproliferative disease in a human or animal in need of the treatment, comprising a step of administering a lymphoproliferative disease treatment effective amount of a composition to said human or animal, wherein the composition comprises β-boswellic acid of at least 5% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 15% by weight and acetyl-11-keto-β-boswellic acid of at least 14% by weight.

141. The method of claim 140, wherein the composition comprises β-boswellic acid of at least 12% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 15% by weight and acetyl-11-keto-β-boswellic acid of at least 14% by weight.

142. The method of claim 141, wherein the composition comprises β-boswellic acid of 12 to 35% by weight, acetyl-β-boswellic acid of 5 to 35% by weight, 11-keto-β-boswellic acid of 15 to 45% by weight and acetyl-11-keto-β-boswellic acid of 14 to 45% by weight.

143. The method of claim 140, wherein the lymphoproliferative disease is leukemia or lymphoma.

144. A method for the prevention of an autoimmune disease in a human or animal in need of the prevention, comprising a step of administering an autoimmune disease prevention effective amount of a composition to said human or animal, wherein the composition comprises β-boswellic acid of at least 5% by weight, acetyl-β-boswellic acid of at least 5% by

weight, 11-keto-β-boswellic acid of at least 15% by weight and acetyl-11-keto-β-boswellic acid of at least 14% by weight.

145. The method of claim 144, wherein the composition comprises β-boswellic acid of at least 12% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 15% by weight and acetyl-11-keto-β-boswellic acid of at least 14% by weight.

146. The method of claim 145, wherein the composition comprises β-boswellic acid of 12 to 35% by weight, acetyl-β-boswellic acid of 5 to 35% by weight, 11-keto-β-boswellic acid of 15 to 45% by weight and acetyl-11-keto-β-boswellic acid of 14 to 45% by weight.

147. The method of claim 144, wherein the autoimmune disease is psoriasis, sarcoidosis, systemic lupus erythematosis, Grave's disease, Hashimoto's thyroiditis, silent thyroiditis, Crohn's disease, Goodpasture syndrome, insulin-dependent diabetes mellitus, insulin-resistant diabetes mellitus, myasthenia gravis, Addison's disease, idiopathic hypoparathyroidism, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, rheumatoid arthritis or scleroderma.

148. A method for the treatment of an autoimmune disease in a human or animal in need of the treatment, comprising a step of administering an autoimmune disease treatment effective amount of a composition to said human or animal, wherein the composition comprises β-boswellic acid of at least 5% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 15% by weight and acetyl-11-keto-β-boswellic acid of at least 14% by weight.

149. The method of claim 148, wherein the composition comprises β-boswellic acid of at least 12% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 15% by weight and acetyl-11-keto-β-boswellic acid of at least 14% by weight.

150. The method of claim 149, wherein the composition comprises β-boswellic acid of 12 to 35% by weight, acetyl-β-boswellic acid of 5 to 35% by weight, 11-keto-β-boswellic acid of 15 to 45% by weight and acetyl-11-keto-β-boswellic acid of 14 to 45% by weight.

151. The method of claim 148, wherein the autoimmune disease is psoriasis, sarcoidosis, systemic lupus erythematosis, Grave's disease, Hashimoto's thyroiditis, silent thyroiditis, Crohn's disease, Goodpasture syndrome, insulin-dependent diabetes mellitus, insulin-resistant diabetes mellitus, myasthenia gravis, Addison's disease, idiopathic hypoparathyroidism, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, rheumatoid arthritis or scleroderma.

152. A process of obtaining boswellic acids comprising the following steps:

(a) providing a *Boswellia serrata* component;

(b) extracting said *Boswellia serrata* component with carbon dioxide to obtain a fluid extract; and

(c) removing carbon dioxide from the fluid extract to obtain the boswellic acids.

153. The process of claim 152, wherein the *Boswellia serrata* component is a gum from *Boswellia serrata*.

154. The process of claim 152, wherein the extracting in step (b) is performed with subcritical extraction.

155. The process of claim 152, wherein the extracting in step (b) is performed with supercritical extraction.

156. A method for the treatment of a tumor in a human or animal in need of the treatment by administering a tumor treating effective amount of a composition to said human or animal, wherein the composition comprises β-boswellic acid of at least 5% by weight, acetyl-β-

boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 15% by weight and acetyl-11-keto-β-boswellic acid of at least 14% by weight.

157. The method of claim 156, wherein the composition comprises β-boswellic acid of at least 12% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 15% by weight and acetyl-11-keto-β-boswellic acid of at least 14% by weight.

158. The method of claim 157, wherein the composition comprises β-boswellic acid of 12 to 35% by weight, acetyl-β-boswellic acid of 5 to 35% by weight, 11-keto-β-boswellic acid of 15 to 45% by weight and acetyl-11-keto-β-boswellic acid of 14 to 45% by weight.

159. A method of inhibiting the synthesis of DNA, RNA and/or protein in a human or animal in need of the inhibition, comprising administering a DNA, RNA and/or protein synthesis inhibition effective amount of β-boswellic acid of at least 5% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 15% by weight or acetyl-11-keto-β-boswellic acid of at least 14% by weight.

160. A method for irreversibly inhibiting the synthesis of DNA in a human or animal in need of the inhibition, comprising administering a DNA synthesis inhibition effective amount of β-boswellic acid of at least 5% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 15% by weight or acetyl-11-keto-β-boswellic acid of at least 14% by weight.

161. A method for preventing or treating a lymphoproliferative disease in a human or animal in need of the prevention or treatment, comprising administering a lymphoproliferative disease preventing or treating effective amount of β-boswellic acid of at least 5% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 15% by weight or acetyl-11-keto-β-boswellic acid of at least 14% by weight.

162. A method for preventing or treating an autoimmune disease in a human or animal in need of the prevention or treatment, comprising administering an autoimmune disease preventing or treating effective amount of β-boswellic acid of at least 5% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 15% by weight or acetyl-11-keto-β-boswellic acid of at least 14% by weight.

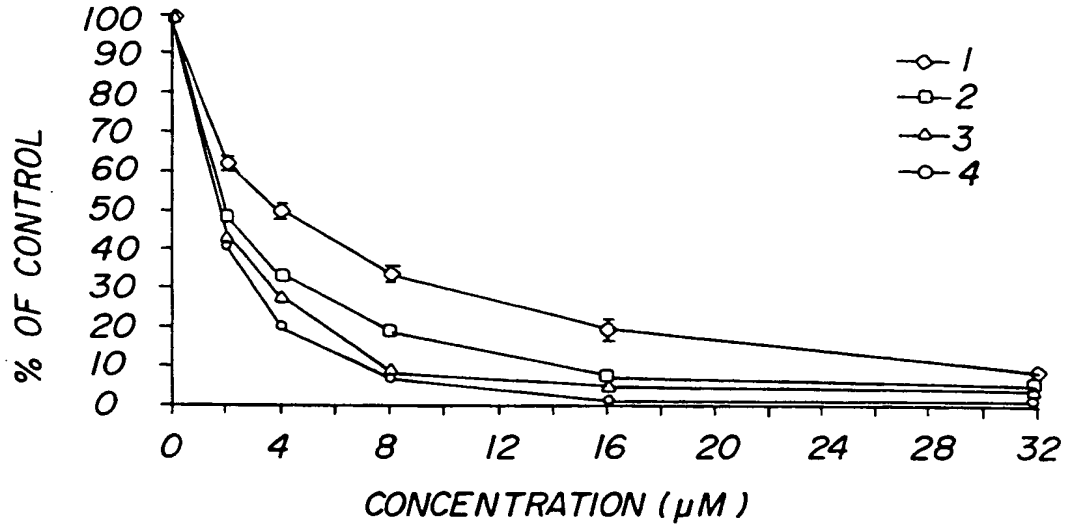
100
90
80
70
60
50
40
30
20
10
0
% OF CONTROL
0
4
8
12
16
20
24
28
32
CONCENTRATION (μM)
1
2
3
4

Fig. 1

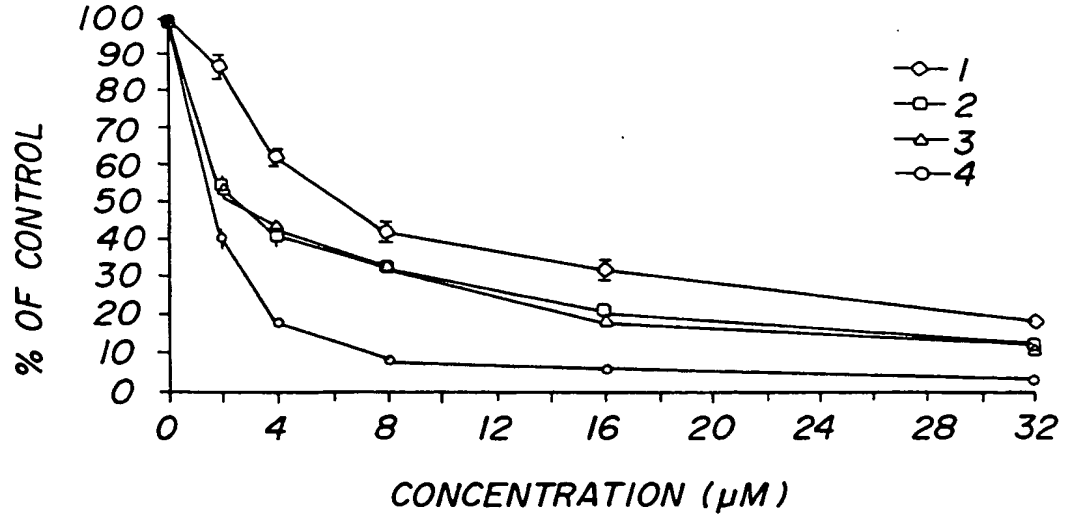
100
90
80
70
60
50
40
30
20
10
0
% OF CONTROL
0
4
8
12
16
20
24
28
32
CONCENTRATION (μM)
1
2
3
4

Fig. 2

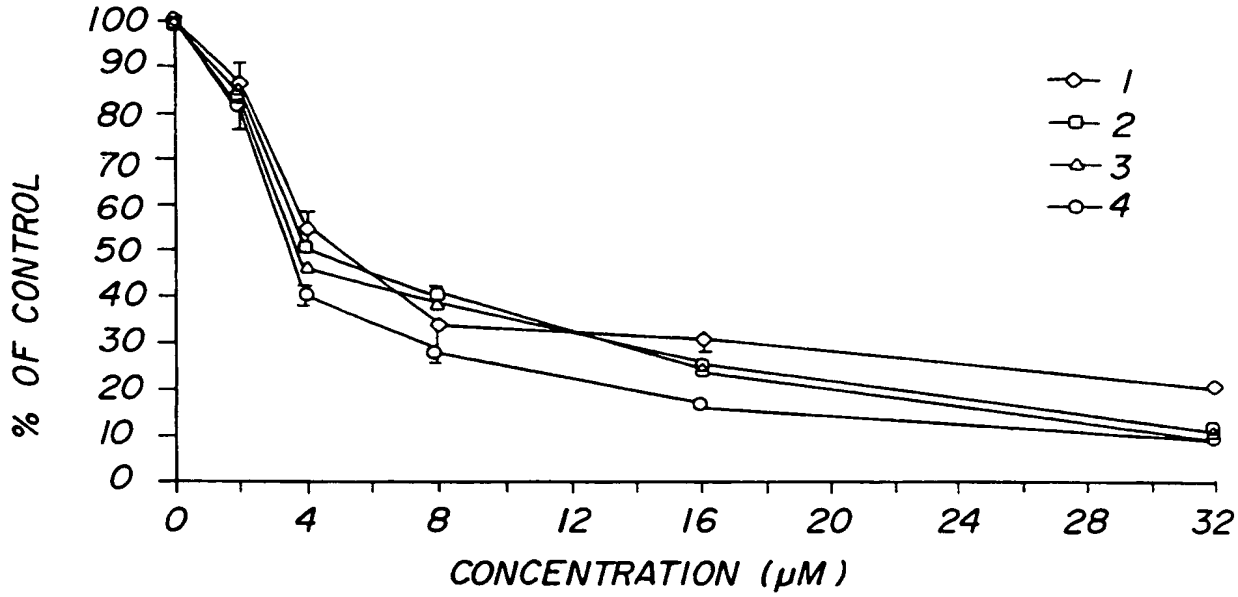
100
90
80
70
60
50
40
30
20
10
0
% OF CONTROL
0
4
8
12
16
20
24
28
32
CONCENTRATION (μM)
1
2
3
4

Fig. 3

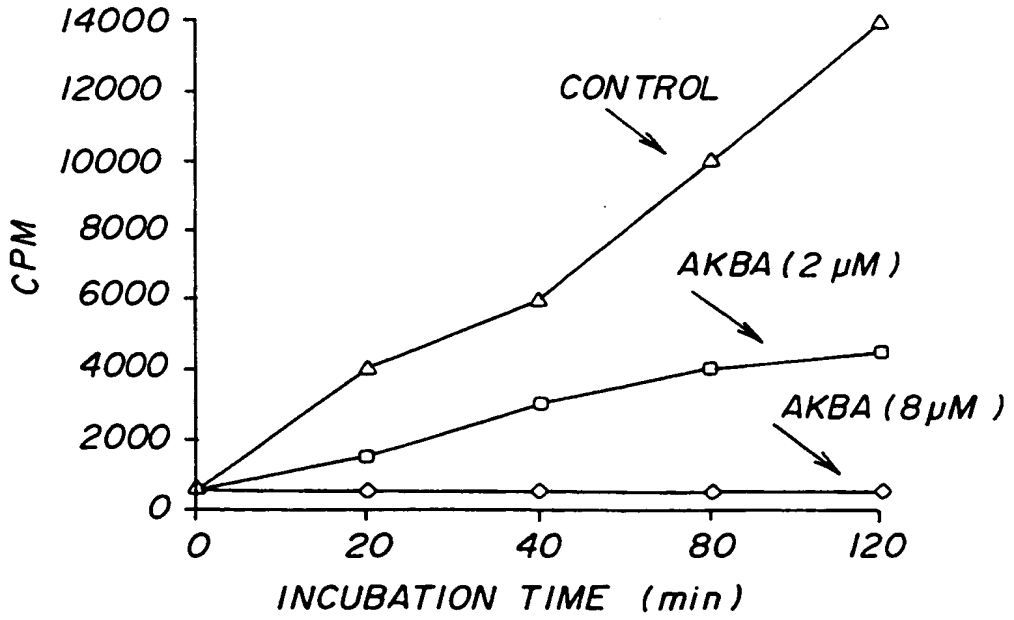
14000
12000
10000
8000
6000
4000
2000
0
CPM
0
20
40
80
120
INCUBATION TIME (min)
CONTROL
AKBA (2 μM)
AKBA (8 μM)

Fig. 4

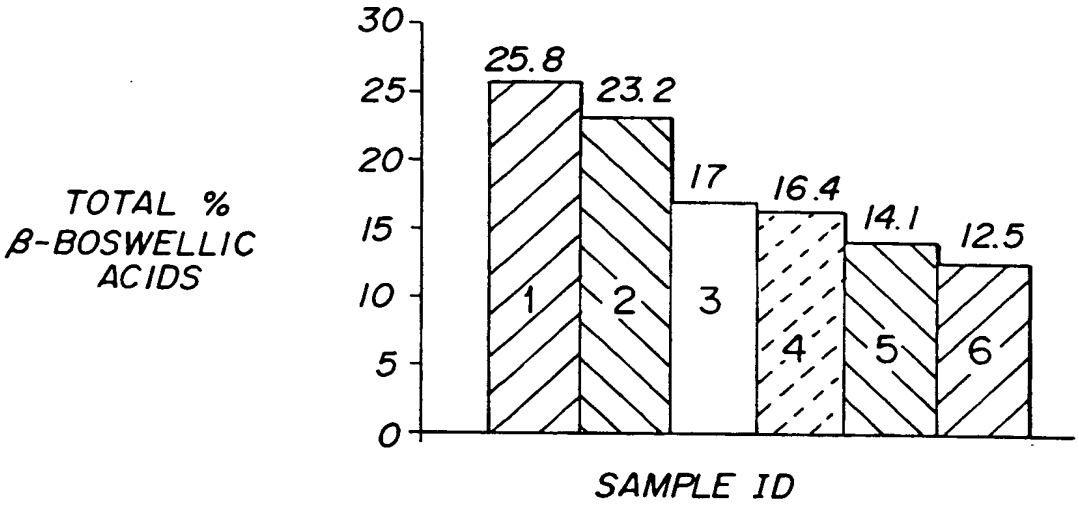
TOTAL % β-BOSWELLIC ACIDS
30
25
20
15
10
5
0
25.8
23.2
17
16.4
14.1
12.5
1
2
3
4
5
6
SAMPLE ID

Fig. 5

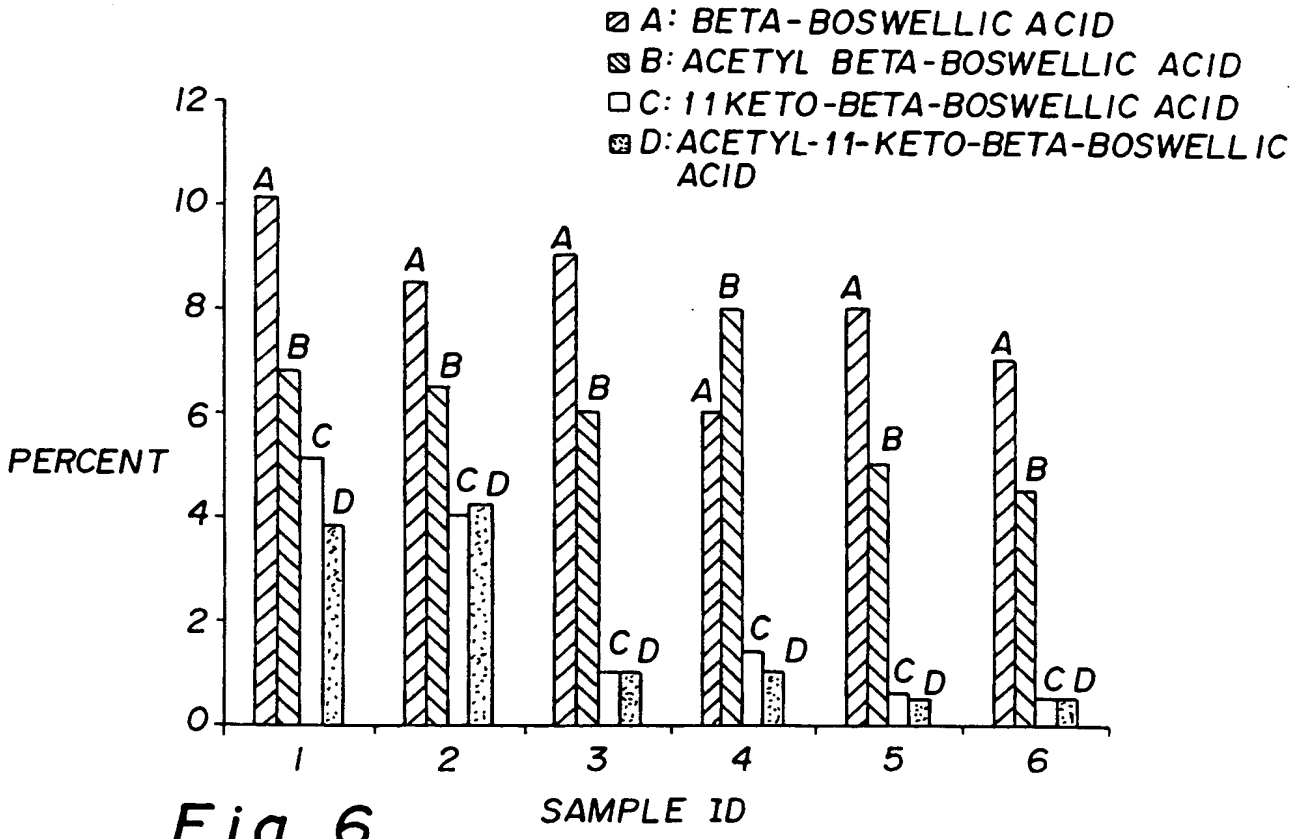
A: BETA-BOSWELLIC ACID
B: ACETYL BETA-BOSWELLIC ACID
C: 11KETO-BETA-BOSWELLIC ACID
D: ACETYL-11-KETO-BETA-BOSWELLIC ACID
PERCENT
12
10
8
6
4
2
0
1
2
3
4
5
6
SAMPLE ID

Fig. 6

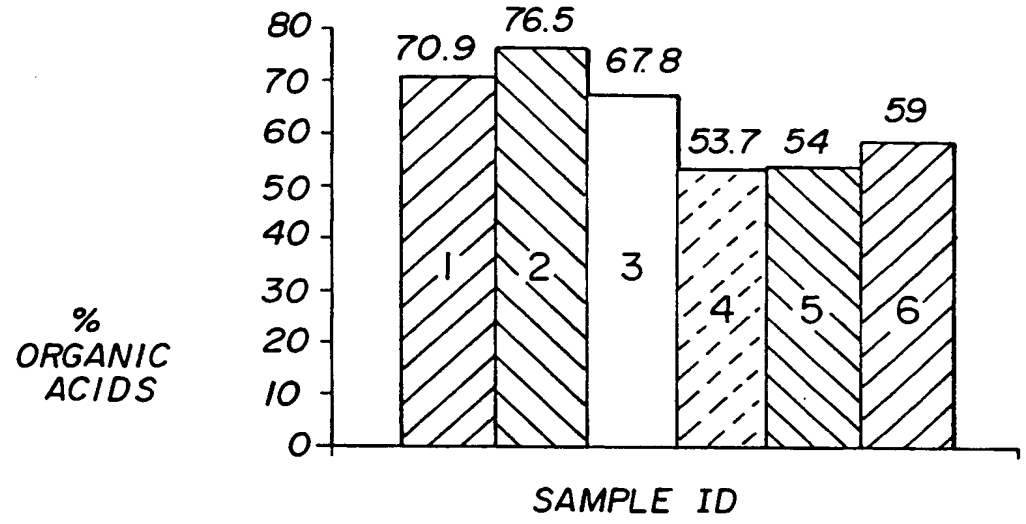
80
70
60
50
40
30
20
10
0
70.9
76.5
67.8
53.7
54
59
1
2
3
4
5
6
% ORGANIC ACIDS
SAMPLE ID

Fig. 7

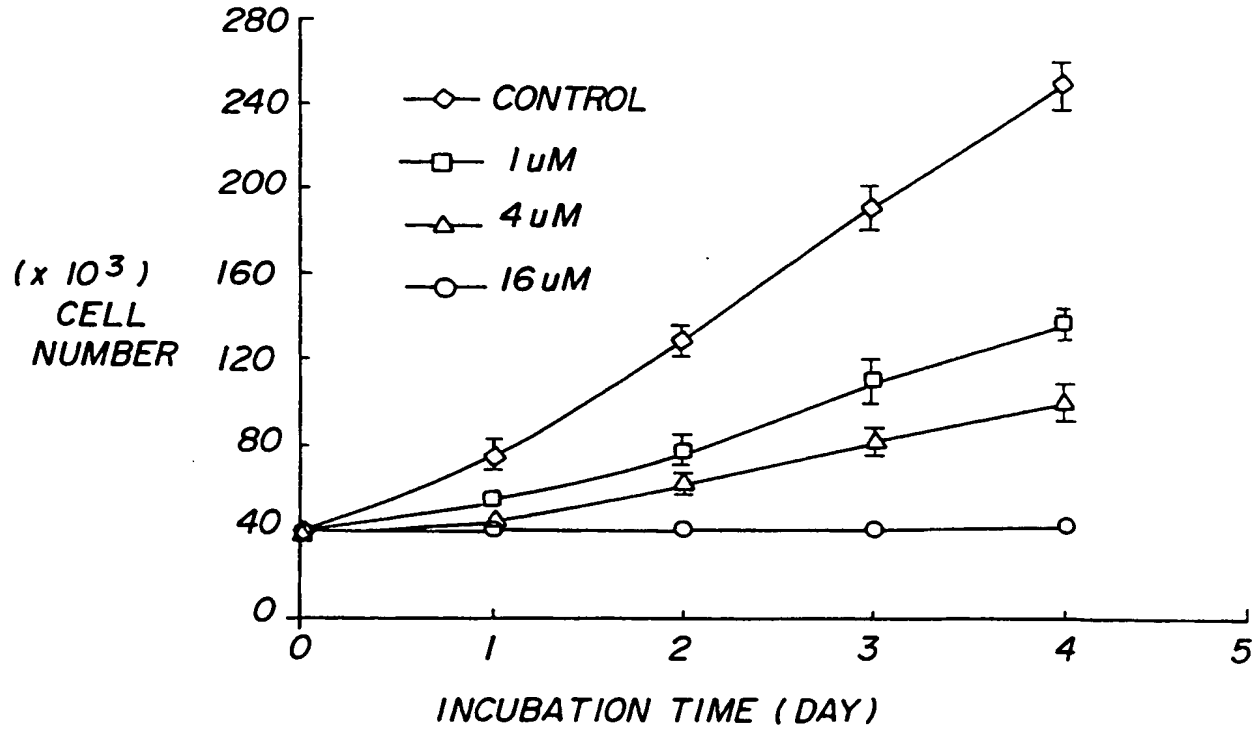
280
240
200
160
120
80
40
0
CONTROL
1uM
4uM
16uM
(x 10³) CELL NUMBER
0
1
2
3
4
5
INCUBATION TIME (DAY)

Fig. 8

claim 86-162 are under article 19

AMENDED CLAIMS
[received by the International Bureau on 15 November 2000 (15.11.00);
original claims 1-85 replaced by new claims 86-162 (13 pages)]

86. A composition consisting essentially of, based on the total weight of the composition, β-boswellic acid of at least 12% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 15% by weight and acetyl-11-keto-β-boswellic acid of at least 14% by weight.

87. The composition of claim 86 consisting essentially of, based on the total weight of the composition, β-boswellic acid of at least 14% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 55% by weight and acetyl-11-keto-β-boswellic acid of at least 14% by weight.

88. The composition of claim 86 consisting essentially of, based on the total weight of the composition, β-boswellic acid of 12 to 35% by weight, acetyl-β-boswellic acid of 5 to 35% by weight, 11-keto-β-boswellic acid of at least 15% by weight and acetyl-11-keto-β-boswellic acid of at least 14% by weight.

89. The composition of claim 88 consisting essentially of, based on the total weight of the composition, β-boswellic acid of 12 to 30% by weight, acetyl-β-boswellic acid of 10 to 25% by weight, 11-keto-β-boswellic acid of at least 15% by weight and acetyl-11-keto-β-boswellic acid of at least 14% by weight.

90. The composition of claim 89 consisting essentially of, based on the total weight of the composition, β-boswellic acid of 14 to 30% by weight, acetyl-β-boswellic acid of 10 to 20% by weight, 11-keto-β-boswellic acid of at least 15% by weight and acetyl-11-keto-β-boswellic acid of at least 14% by weight.

91. The composition of claim 88 consisting essentially of, based on the total weight of the composition, β-boswellic acid of 14 to 35% by weight, acetyl-β-boswellic acid of 10 to 20%

by weight, 11-keto-β-boswellic acid of at least 15% by weight and acetyl-11-keto-β-boswellic acid of at least 14% by weight.

92. The composition of claim 88 consisting essentially of, based on the total weight of the composition, β-boswellic acid of 14 to 35% by weight, acetyl-β-boswellic acid of 10 to 20% by weight, 11-keto-β-boswellic acid of at least 15% by weight and acetyl-11-keto-β-boswellic acid of at least 14% by weight.

93. The composition of claim 86, wherein the β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid are derived from any natural source.

94. A composition comprising three boswellic acids selected from the group consisting of β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid, wherein, based on the total weight of the composition, the amount of β-boswellic acid is at least 5% by weight, the amount of acetyl-β-boswellic acid of is least 5% by weight, the amount of 11-keto-β-boswellic acid is at least 15% by weight, and the amount of acetyl-11-keto-β-boswellic acid is at least 14% by weight.

95. The composition of claim 94, wherein the amount of β-boswellic acid is 14 to 65% by weight, the amount of acetyl-β-boswellic acid is 5 to 65% by weight, the amount of 11-keto-β-boswellic acid is 15 to 60% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 14 to 60% by weight.

96. The composition of claim 95, wherein the amount of β-boswellic acid is 14 to 55% by weight, the amount of acetyl-β-boswellic acid is 10 to 55% by weight, the amount of 11-keto-β-boswellic acid is 15 to 50% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 14 to 50% by weight.

97. The composition of claim 96, wherein the amount of β-boswellic acid is 14 to 35% by weight, the amount of acetyl-β-boswellic acid is 10 to 35% by weight, the amount of 11-keto-β-boswellic acid is 15 to 40% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 14 to 40% by weight.

98. The composition of claim 94, wherein the β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid are derived from any natural source.

99. A composition comprising two boswellic acids selected from the group consisting of β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid, wherein, based on the total weight of the composition, the amount of β-boswellic acid is 1 to 34% or at least 56% by weight, the amount of acetyl-β-boswellic acid is 1 to 24% or at least 46% by weight, the amount of 11-keto-β-boswellic acid is at least 15% by weight, and the amount of acetyl-11-keto-β-boswellic acid is at least 14% by weight.

100. The composition of claim 99, wherein the amount of β-boswellic acid is 1 to 34% or 56 to 95% by weight, the amount of acetyl-β-boswellic acid is 1 to 24% or 46 to 95% by weight, the amount of 11-keto-β-boswellic acid is 15 to 95% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 14 to 95% by weight.

101. The composition of claim 100, wherein the amount of β-boswellic acid is 1 to 34% or 56 to 70% by weight, the amount of acetyl-β-boswellic acid is 1 to 24% or 46 to 70% by weight, the amount of 11-keto-β-boswellic acid is 30 to 70% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 30 to 70% by weight.

102. The composition of claim 101, wherein the amount of β-boswellic acid is 1 to 34% or 40 to 60% by weight, the amount of acetyl-β-boswellic acid is 1 to 24% or 40 to 60% by weight, the amount of 11-keto-β-boswellic acid is 40 to 60% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 40 to 60% by weight.

103. The composition of claim 99, wherein the β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid are derived from any natural source.

104. A composition comprising boswellic acids, wherein the boswellic acids consist of three substances selected from the group consisting of β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid, wherein, based on the total weight of the composition, the amount of β-boswellic acid is at least 5% by weight, the amount of acetyl-β-boswellic acid of is least 5% by weight, the amount of 11-keto-β-boswellic acid is at least 15% by weight, and the amount of acetyl-11-keto-β-boswellic acid is at least 14% by weight.

105. The composition of claim 104, wherein the amount of β-boswellic acid is 5 to 65% by weight, the amount of acetyl-β-boswellic acid is 5 to 65% by weight, the amount of 11-keto-β-boswellic acid is 15 to 65% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 14 to 65% by weight.

106. The composition of claim 105, wherein the amount of β-boswellic acid is 15 to 55% by weight, the amount of acetyl-β-boswellic acid is 15 to 55% by weight, the amount of 11-keto-β-boswellic acid is 15 to 55% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 15 to 55% by weight.

107. The composition of claim 106, wherein the amount of β-boswellic acid is 20 to 40% by weight, the amount of acetyl-β-boswellic acid is 20 to 40% by weight, the amount of 11-keto-β-boswellic acid is 20 to 40% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 20 to 40% by weight.

108. The composition of claim 104, wherein the β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid are derived from any natural source.

109. A composition comprising boswellic acids, wherein the boswellic acids consist of two substances selected from the group consisting of β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid, wherein, based on the total weight of the boswellic acids, the amount of β-boswellic acid is 1 to 34% or at least 56% by weight, the amount of acetyl-β-boswellic acid of is 1 to 24% or at least 46% by weight, the amount of 11-keto-β-boswellic acid is at least 15% by weight, and the amount of acetyl-11-keto-β-boswellic acid is at least 14% by weight.

110. The composition of claim 109, wherein the amount of β-boswellic acid is 1 to 34% or 56 to 90% by weight, the amount of acetyl-β-boswellic acid is 1 to 24% or 46 to 90% by weight, the amount of 11-keto-β-boswellic acid is 15 to 90% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 14 to 90% by weight.

111. The composition of claim 110, wherein the amount of β-boswellic acid is 1 to 34% or 56 to 80% by weight, the amount of acetyl-β-boswellic acid is 1 to 24% or 46 to 80% by weight, the amount of 11-keto-β-boswellic acid is 20 to 80% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 20 to 80% by weight.

112. The composition of claim 111, wherein the amount of β-boswellic acid is 1 to 34% or 56 to 70% by weight, the amount of acetyl-β-boswellic acid is 1 to 24% or 46 to 70% by weight, the amount of 11-keto-β-boswellic acid is 30 to 70% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 30 to 70% by weight.

113. The composition of claim 112, wherein the amount of β-boswellic acid is 1 to 34% or 56 to 60% by weight, the amount of acetyl-β-boswellic acid is 1 to 24% or 46 to 60% by weight, the amount of 11-keto-β-boswellic acid is 40 to 60% by weight, and the amount of acetyl-11-keto-β-boswellic acid is 40 to 60% by weight.

114. The composition of claim 94, wherein two of the three boswellic acids are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

115. The composition of claim 94, wherein two of the three boswellic acids are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

116. The composition of claim 96, wherein two of the three boswellic acids are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

117. The composition of claim 97, wherein two of the three boswellic acids are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

118. The composition of claim 99, wherein the two boswellic acids are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

119. The composition of claim 100, wherein the two boswellic acids are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

120. The composition of claim 101, wherein the two boswellic acids are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

121. The composition of claim 102, wherein the two boswellic acids are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

122. The composition of claim 104, wherein two of the three substances are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

123. The composition of claim 105, wherein two of the three substances are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

124. The composition of claim 106, wherein two of the three substances are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

125. The composition of claim 107, wherein two of the three substances are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

126. The composition of claim 109, wherein the two substances are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

127. The composition of claim 110, wherein the two substances are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

128. The composition of claim 111, wherein the two substances are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

129. The composition of claim 112, wherein the two substances are 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

130. A method for inhibition of DNA, RNA and/or protein synthesis in a human or animal in need of the inhibition, comprising a step of administering a DNA, RNA and/or protein synthesis inhibition effective amount of a composition to said human or animal, wherein the composition comprises β-boswellic acid of at least 5% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 15% by weight and acetyl-11-keto-β-boswellic acid of at least 14% be weight.

131. The method of claim 130, wherein the composition comprises β-boswellic acid of at least 12% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 15% by weight and acetyl-11-keto-β-boswellic acid of at least 14% by weight.

132. The method of claim 131, wherein the composition comprises β-boswellic acid of 12 to 35% by weight, acetyl-β-boswellic acid of 5 to 35% by weight, 11-keto-β-boswellic acid of 15 to 45% by weight and acetyl-11-keto-β-boswellic acid of 14 to 45% by weight.

133. A method for irreversible inhibition of DNA synthesis in a human or animal in need of the inhibition, comprising a step of administering a DNA inhibition effective amount of a composition to said human or animal, wherein the composition comprises β-boswellic acid of at least 5% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 15% be weight and acetyl-11-keto-β-boswellic acid of at least 14% be weight.

134. The method of claim 133, wherein the composition comprises β-boswellic acid of at least 12% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 15% by weight and acetyl-11-keto-β-boswellic acid of at least 14% by weight.

135. The method of claim 134, wherein the composition comprises β-boswellic acid of 12 to 35% by weight, acetyl-β-boswellic acid of 5 to 35% by weight, 11-keto-β-boswellic acid of 15 to 45% by weight and acetyl-11-keto-β-boswellic acid of 14 to 45% by weight.

136. A method for the prevention of a lymphoproliferative disease in a human or animal in need of the prevention, comprising a step of administering a lymphoproliferative disease prevention effective amount of a composition to said human or animal, wherein the composition comprises β-boswellic acid of at least 5% be weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 15% be weight and acetyl-11-keto-β-boswellic acid of at least 14% by weight.

137. The method of claim 136, wherein the composition comprises β-boswellic acid of at least 12% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 15% by weight and acetyl-11-keto-β-boswellic acid of at least 14% by weight.

138. The method of claim 137, wherein the composition comprises β-boswellic acid of 12 to 35% by weight, acetyl-β-boswellic acid of 5 to 35% by weight, 11-keto-β-boswellic acid of 15 to 45% by weight and acetyl-11-keto-β-boswellic acid of 14 to 45% by weight.

139. The method of claim 136, wherein the lymphoproliferative disease is leukemia or lymphoma.

140. A method for the treatment of a lymphoproliferative disease in a human or animal in need of the treatment, comprising a step of administering a lymphoproliferative disease treatment effective amount of a composition to said human or animal, wherein the composition comprises β-boswellic acid of at least 5% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 15% by weight and acetyl-11-keto-β-boswellic acid of at least 14% by weight.

141. The method of claim 140, wherein the composition comprises β-boswellic acid of at least 12% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 15% by weight and acetyl-11-keto-β-boswellic acid of at least 14% by weight.

142. The method of claim 141, wherein the composition comprises β-boswellic acid of 12 to 35% by weight, acetyl-β-boswellic acid of 5 to 35% by weight, 11-keto-β-boswellic acid of 15 to 45% by weight and acetyl-11-keto-β-boswellic acid of 14 to 45% by weight.

143. The method of claim 140, wherein the lymphoproliferative disease is leukemia or lymphoma.

144. A method for the prevention of an autoimmune disease in a human or animal in need of the prevention, comprising a step of administering an autoimmune disease prevention effective amount of a composition to said human or animal, wherein the composition comprises β-boswellic acid of at least 5% by weight, acetyl-β-boswellic acid of at least 5% by

weight, 11-keto-β-boswellic acid of at least 15% by weight and acetyl-11-keto-β-boswellic acid of at least 14% by weight.

145. The method of claim 144, wherein the composition comprises β-boswellic acid of at least 12% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 15% by weight and acetyl-11-keto-β-boswellic acid of at least 14% by weight.

146. The method of claim 145, wherein the composition comprises β-boswellic acid of 12 to 35% by weight, acetyl-β-boswellic acid of 5 to 35% by weight, 11-keto-β-boswellic acid of 15 to 45% by weight and acetyl-11-keto-β-boswellic acid of 14 to 45% by weight.

147. The method of claim 144, wherein the autoimmune disease is psoriasis, sarcoidosis, systemic lupus erythematosis, Grave's disease, Hashimoto's thyroiditis, silent thyroiditis, Crohn's disease, Goodpasture syndrome, insulin-dependent diabetes mellitus, insulin-resistant diabetes mellitus, myasthenia gravis, Addison's disease, idiopathic hypoparathyroidism, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, rheumatoid arthritis or scleroderma.

148. A method for the treatment of an autoimmune disease in a human or animal in need of the treatment, comprising a step of administering an autoimmune disease treatment effective amount of a composition to said human or animal, wherein the composition comprises β-boswellic acid of at least 5% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 15% by weight and acetyl-11-keto-β-boswellic acid of at least 14% by weight.

149. The method of claim 148, wherein the composition comprises β-boswellic acid of at least 12% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 15% by weight and acetyl-11-keto-β-boswellic acid of at least 14% by weight.

150. The method of claim 149, wherein the composition comprises β-boswellic acid of 12 to 35% by weight, acetyl-β-boswellic acid of 5 to 35% by weight, 11-keto-β-boswellic acid of 15 to 45% by weight and acetyl-11-keto-β-boswellic acid of 14 to 45% by weight.

151. The method of claim 148, wherein the autoimmune disease is psoriasis, sarcoidosis, systemic lupus erythematosis, Grave's disease, Hashimoto's thyroiditis, silent thyroiditis, Crohn's disease, Goodpasture syndrome, insulin-dependent diabetes mellitus, insulin-resistant diabetes mellitus, myasthenia gravis, Addison's disease, idiopathic hypoparathyroidism, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, rheumatoid arthritis or scleroderma.

152. A process of obtaining boswellic acids comprising the following steps:

(a) providing a *Boswellia serrata* component;

(b) extracting said *Boswellia serrata* component with carbon dioxide to obtain a fluid extract; and

(c) removing carbon dioxide from the fluid extract to obtain the boswellic acids.

153. The process of claim 152, wherein the *Boswellia serrata* component is a gum from *Boswellia serrata*.

154. The process of claim 152, wherein the extracting in step (b) is performed with subcritical extraction.

155. The process of claim 152, wherein the extracting in step (b) is performed with supercritical extraction.

156. A method for the treatment of a tumor in a human or animal in need of the treatment by administering a tumor treating effective amount of a composition to said human or animal, wherein the composition comprises β-boswellic acid of at least 5% by weight, acetyl-β-

boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 15% by weight and acetyl-11-keto-β-boswellic acid of at least 14% by weight.

157. The method of claim 156, wherein the composition comprises β-boswellic acid of at least 12% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 15% by weight and acetyl-11-keto-β-boswellic acid of at least 14% by weight.

158. The method of claim 157, wherein the composition comprises β-boswellic acid of 12 to 35% by weight, acetyl-β-boswellic acid of 5 to 35% by weight, 11-keto-β-boswellic acid of 15 to 45% by weight and acetyl-11-keto-β-boswellic acid of 14 to 45% by weight.

159. A method of inhibiting the synthesis of DNA, RNA and/or protein in a human or animal in need of the inhibition, comprising administering a DNA, RNA and/or protein synthesis inhibition effective amount of β-boswellic acid of at least 5% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 15% by weight or acetyl-11-keto-β-boswellic acid of at least 14% by weight.

160. A method for irreversibly inhibiting the synthesis of DNA in a human or animal in need of the inhibition, comprising administering a DNA synthesis inhibition effective amount of β-boswellic acid of at least 5% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 15% by weight or acetyl-11-keto-β-boswellic acid of at least 14% by weight.

161. A method for preventing or treating a lymphoproliferative disease in a human or animal in need of the prevention or treatment, comprising administering a lymphoproliferative disease preventing or treating effective amount of β-boswellic acid of at least 5% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 15% by weight or acetyl-11-keto-β-boswellic acid of at least 14% by weight.

162. A method for preventing or treating an autoimmune disease in a human or animal in need of the prevention or treatment, comprising administering an autoimmune disease preventing or treating effective amount of β-boswellic acid of at least 5% by weight, acetyl-β-boswellic acid of at least 5% by weight, 11-keto-β-boswellic acid of at least 15% by weight or acetyl-11-keto-β-boswellic acid of at least 14% by weight.

RBM

PATENT COOPERATION TREATY

Received

PCT

Fox

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

MURRAY, Robert B.
Arent Fox Kintner Plotkin & Kahn
PLLC
1050 Connecticut Avenue, N.W.
Suite 600
Washington, DC 20036-5339
ETATS-UNIS D'AMERIQUE

WRITTEN OPINION

(PCT Rule 66)

Date of mailing *(day/month/year)*	06.04.2001
Applicant's or agent's file reference: F108064-0000	**REPLY DUE** **within 2 month(s)** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/08217	28/04/2000	30/04/1999

International Patent Classification (IPC) or both national classification and IPC

A61K31/19

Applicant

SABINSA CORPORATION et al.

1. This written opinion is the **second** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain document cited
VII	☐	Certain defects in the international application
VIII	☒	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 30/08/2001.

Name and mailing address of the international preliminary examining authority:
European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer / Examiner
Schnack, A

Formalities officer (incl. extension of time limits)
Hundt, D
Telephone No. +49 89 2399 8042

I. Basis of the opinion

1. With regard to the **elements** of the international application (Replacement *sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed"*):

Description, pages:

1-25 as originally filed

Claims, No.:

1-85 as originally filed

Drawings, sheets:

1/4-4/4 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application,

☒ claims Nos. 45-66, 79-85,

because:

☒ the said international application, or the said claims Nos. 45-66, 79-85 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-85 (no)
Inventive step (IS)	Claims	1-85 (no)

Industrial applicability (IA) Claims 1-44, 67-78, (yes)

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Reference is made to the following documents:

D1: EP 0 755 940
D2: EP 0 552 657
D3: Patent Abstracts of Japan, vol. 017, no. 100.
D4: WO 90 019 37
D5: Deutsche Apotheker Zeitung, (139/11) pp. 39-40
D6: Pharmazeutische Zeitung, (1997) 142/39, (pp. 1-20)
D7: Planta Medica, vol. 64, no. 4, 1998, pp. 328-331

Section III
Non-establishments of opinion:

Claims 45-66 and 79-85 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Section V
V.1. Novelty
Remarks under Article 33(2) PCT:

Compositions comprising the present boswellic acids and uses thereof are already known, (see at least D1-D4, the passages mentioned in the search report). Thus, the subject matter according to present claims 1-44 appears to lack novelty with respect to these documents.

The present methods for obtaining the present boswellic acids are also known from D1, (see D1, claims 3-11). Thus, the subject matter of present claims 67-78 appears to lack novelty with respect to D1. Also the extracts and powders according to D2-D4 must have been obtained by a process at least very similar to the present process.

The present medical uses, (inhibition of DNA, RNA or protein synthesis, autoimmune diseases, cancer treatment and lymphoproliferative diseases), of the present

compounds are also known, (see D5, the entire document, which discloses the therapeutic effect in cancer treatment, D6, the passages mentioned in the search report, which discloses cancer treatment, rheumatoid arthritis and inhibition of DNA synthesis, and D7, which discloses treatment of leukemia and inhibition of DNA synthesis). Thus, the subject matter according to present claims 45-66 and 79-85 appears to lack novelty with resect to these documents.

V.2. Inventive step

Remarks under Article 33(3) PCT:

It is not considered to be inventive to arbitrary select specific amounts of the four known active components in a composition for treating diseases known to be treatable with the present compounds.

No other inventive features can be seen in the present subject matter.

V.3 Industrial applicability

Remarks under Article 33(4) PCT:

For the assessment of the present claims 45-66 and 79-85 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Section VIII

The present claim are inconcise contrary to article 6 PCT, because there are too many independent claims: (claims 1, 9, 14, 19 and 24 all relate to compositions comprising one or more of the active components and claims 45, 48, 51, 55, 59, 63, 79, 82, 83, 84 and 85 all relate to treatment of different diseases). This number of independent claims in the same category is considered to be far more than acceptable under Article 6 PCT.

Usually only one independent claim in each category is considered allowable under Article 6 PCT, unless special circumstances are present, which do not appear to be the case presently.

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line

IPEA/ EP

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only

Identification of IPEA	Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION

Applicant's or agent's file reference: F108064-0000

International application No.	International filing date *(day/month/year)*	(Earliest) Priority date *(day/month/year)*
PCT/US00/08217	28 April 2000 (28/04/00)	30 April 1999 (30/04/99)

Title of invention
COMPOSITIONS OF BOSWELLIC ACIDS DERIVED FROM BOSWELLIA SERRATA GUM RESIN, FOR TREATING LYMPHOPROLIFERATIVE AND AUTOIMMUNE CONDITIONS

Box No. II APPLICANT(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

SABINSA CORPORATION
121 Ethel Road West, Unit 6
Piscataway, New Jersey 08854
US

Telephone No.: (732) 777-1111
Facsimile No.: (732) 777-1443
Teleprinter No.:

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
US	US

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

MAJEED, Muhammed
121 Ethel Road West, Unit 6
Piscataway, New Jersey 08854
US

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
US	US

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

BADMAEV, Vladimir
121 Ethel Road West, Unit 6
Piscataway, New Jersey 08854
US

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
US	US

☐ Further applicants are indicated on a continuation sheet.

International application No.
PCT/US00/08217

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is ☒ agent ☐ common representative

and ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.

☐ is hereby appointed and any earlier appointment of (an) agent(s) /common representative is hereby revoked.

☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official The address must include postal code and name of country.)*

MURRAY, Robert B.
Arent Fox Kintner Plotkin & Kahn, PLLC
1050 Connecticut Avenue, NW, Suite 600
Washington, DC 20036-5339
US

Telephone No.:
(202) 857-6383

Facsimile No.:
(202) 638-4810

Teleprinter No.:

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination **to start on the basis of:**

☐ the international application as originally filed.

the description ☒ as originally filed
☐ as amended under Article 34

the claims ☐ as originally filed
☒ as amended under Article 19 (together with any accompanying statement)
☒ as amended under Article 34

the drawings ☒ as originally filed
☐ as amended under Article 34

2. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. ☐ The applicant wishes the start of the international preliminary examination **to be postponed** until the expiration of 20 months from the priority date unless the International Preliminary Examing Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English

☒ which is the language in which the international application was filed.
☐ which is the language of a translation furnished for the purposes of international search.
☐ which is the language of publication of the international application.
☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The applicant hereby **elects all eligible States** *(that is, all States which have been designated and which are bound by Chapter II of the PCT)*

excluding the following States which the applicant wishes **not to elect:**

Sheet No. 3

International application No.
PCT/US00/08217

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:			For International Preliminary Examining Authority use only: received	not received
1. translation of international application	:	sheets	☐	☐
2. amendments under Article 34	:	2 sheets	☐	☐
3. copy (or where required, translation) of amendments under Article 19	:	sheets	☐	☐
4. copy (or, where required, translation) of statement under Article 19	:	sheets	☐	☐
5. letter	:	1 sheets	☐	☐
6. other *(specify)* Cover Letter	:	2 sheets	☐	☐

The demand is also accompanied by the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ nucleotide and or amino acid sequence listing in computer readable form
6. ☐ other *(specify)*:

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

MURRAY, Robert B.
MARKMONITOR, CHARGE

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:
2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):
3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. ☐ The applicant has been informed accordingly.
4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.
5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

CHAPTER II

PCT

FEE CALCULATION SHEET

Annex to the Demand for international preliminary examination

International application No.	PCT/US00/08217
Applicant's or agent's file reference	F108064-0000

For International Preliminary Examining Authority use only

Date stamp of the IPEA

Applicant

Sabinsa Corporation, et al.

Calculation of prescribed fees

1. Preliminary examination fee	1,533.00	P
2. Handling fee *(Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.)*	147.00	H
3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box	1,680.00	TOTAL

Mode of Payment

☐	authorization to charge deposit account with the IPEA (see below)	☐	cash
☒	cheque	☐	revenue stamps
☐	postal money order	☐	coupons
☐	bank draft	☐	other *(specify)*:

Deposit Account Authorization *(this mode of payment may not be available at all IPEAs)*

The IPEA/ _____ ☐ is hereby authorized to charge the total fees indicated above to my deposit account.

☐ *(this check-box may be marked only if the conditions for deposit accounts of the IPEA so permit)* is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.

Deposit Account Number	Date *(day/month/year)*	Signature

PATENT COOPERATION TREATY

Received

JUN - 5 2001

Arent Fox

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

RBM

To:

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PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	28.06.2001
Applicant's or agent's file reference F108064-0000 3	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/08217	28/04/2000	30/04/1999

Applicant
SABINSA CORPORATION et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Exner, K Tel.+49 89 2399-7826

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
F108064-0000		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/08217	28/04/2000	30/04/1999
International Patent Classification (IPC) or national classification and IPC A61K31/19		
Applicant SABINSA CORPORATION et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
30/11/2000	28.06.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Schnack, A Telephone No. +49 89 2399 8149

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/08217

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-25 as originally filed

Claims, No.:

1-85 as originally filed

Drawings, sheets:

1/4-4/4 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 45-66, 79-85.

because:

☒ the said international application, or the said claims Nos. 45-66, 79-85 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N) Yes: Claims none

	No:	Claims	1-85
Inventive step (IS)	Yes:	Claims	none
	No:	Claims	1-85
Industrial applicability (IA)	Yes:	Claims	1-44, 67-78 (for claims 45-66 and 79-85: see seperate sheet)
	No:	Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Reference is made to the following documents:

D1: EP 0 755 940
D2: EP 0 552 657
D3: Patent Abstracts of Japan, vol. 017, no. 100.
D4: WO 90 019 37
D5: Deutsche Apotheker Zeitung, (139/11) pp. 39-40
D6: Pharmazeutische Zeitung, (1997) 142/39, (pp. 1-20)
D7: Planta Medica, vol. 64, no. 4, 1998, pp. 328-331

Section III
Non-establishments of opinion:

Claims 45-66 and 79-85 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Section V
V.1. Novelty
Remarks under Article 33(2) PCT:

Compositions comprising the present boswellic acids and uses thereof are already known, (see at least D1-D4, the passages mentioned in the search report). Thus, the subject matter according to present claims 1-44 appears to lack novelty with respect to these documents.

The present methods for obtaining the present boswellic acids are also known from D1, (see D1, claims 3-11). Thus, the subject matter of present claims 67-78 appears to lack novelty with respect to D1. Also the extracts and powders according to D2-D4 must have been obtained by a process at least very similar to the present process.

The present medical uses, (inhibition of DNA, RNA or protein synthesis, autoimmune diseases, cancer treatment and lymphoproliferative diseases), of the present

compounds are also known, (see D5, the entire document, which discloses the therapeutic effect in cancer treatment, D6, the passages mentioned in the search report, which discloses cancer treatment, rheumatoid arthritis and inhibition of DNA synthesis, and D7, which discloses treatment of leukemia and inhibition of DNA synthesis). Thus, the subject matter according to present claims 45-66 and 79-85 appears to lack novelty with resect to these documents.

V.2. Inventive step

Remarks under Article 33(3) PCT:

It is not considered to be inventive to arbitrary select specific amounts of the four known active components in a composition for treating diseases known to be treatable with the present compounds.

No other inventive features can be seen in the present subject matter.

V.3 Industrial applicability

Remarks under Article 33(4) PCT:

For the assessment of the present claims 45-66 and 79-85 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Section VIII

The present claim are inconcise contrary to Article 6 PCT, because there are too many independent claims: (claims 1, 9, 14, 19 and 24 all relate to compositions comprising one or more of the active components and claims 45, 48, 51, 55, 59, 63, 79, 82, 83, 84 and 85 all relate to treatment of different diseases). This number of independent claims in the same category is considered to be far more than acceptable under Article 6 PCT.

Usually only one independent claim in each category is considered allowable under Article 6 PCT, unless special circumstances are present, which do not appear to be the case presently.

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For Receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* F108064-00003

Box No. I TITLE OF INVENTION

Method of Treatment of Lymphoproliferative and Autoimmune Conditions with New Composition of Boswellic Acids Derived from Boswellia serrata Gum Resin

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

SABINSA CORPORATION
121 Ethel Road West, Unit 6
Piscataway, New Jersey 08854
US

☐ This person is also inventor.

Telephone No.
(732) 777-1111

Facsimile No.
(732) 777-1443

Teleprinter No.

State *(that is, country)* of nationality:
US

State *(that is, country)* of residence:
US

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

MAJEED, Muhammed
121 Ethel Road West, Unit 6
Piscataway, New Jersey 08854
US

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:
US

State *(that is, country)* of residence:
US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

MURRAY, Robert B.
Arent Fox Kintner Plotkin & Kahn, PLLC
1050 Connecticut Avenue, NW, Suite 600
Washington, DC 20036-5339
US

Telephone No.
(202) 857-6383

Facsimile No.
(202) 638-4810

Teleprinter No.

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet is not to be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

BADMAEV, Vladimir
121 Ethel Road West, Unit 6
Piscataway, New Jersey 08854
US

This person is:

- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:

- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:

- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:

- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked):*

Regional Patent

☒ **AP ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT

☒ **EA Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian

☒ **EP European Patent:** AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT

☒ **OA OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line):*

☒	AE	United Arab Emirates	☒	LR	Liberia
☒	AL	Albania	☒	LS	Lesotho
☒	AM	Armenia	☒	LT	Lithuania
☒	AT	Austria	☒	LU	Luxembourg
☒	AU	Australia	☒	LV	Latvia
☒	AZ	Azerbaijan	☒	MA	Morocco
☒	BA	Bosnia and Herzegovina	☒	MD	Republic of Moldova
☒	BB	Barbados	☒	MG	Madagascar
☒	BG	Bulgaria	☒	MK	The former Yugoslav Republic of Macedonia
☒	BR	Brazil			
☒	BY	Belarus	☒	MN	Mongolia
☒	CA	Canada	☒	MW	Malawi
☒	CH and LI	Switzerland and Liechtenstein	☒	MX	Mexico
☒	CN	China	☒	NO	Norway
☒	CR	Costa Rica	☒	NZ	New Zealand
☒	CU	Cuba	☒	PL	Poland
☒	CZ	Czech Republic	☒	PT	Portugal
☒	DE	Germany	☒	RO	Romania
☒	DK	Denmark	☒	RU	Russian Federation
☒	DM	Dominica	☒	SD	Sudan
☒	EE	Estonia	☒	SE	Sweden
☒	ES	Spain	☒	SG	Singapore
☒	FI	Finland	☒	SI	Slovenia
☒	GB	United Kingdom	☒	SK	Slovakia
☒	GD	Grenada	☒	SL	Sierra Leone
☒	GE	Georgia	☒	TJ	Tajikistan
☒	GH	Ghana	☒	TM	Turkmenistan
☒	GM	Gambia	☒	TR	Turkey
☒	HR	Croatia	☒	TT	Trinidad and Tobago
☒	HU	Hungary	☒	TZ	United Republic of Tanzania
☒	ID	Indonesia	☒	UA	Ukraine
☒	IL	Israel	☒	UG	Uganda
☒	IN	India	☒	US	United States of America
☒	IS	Iceland			
☒	JP	Japan	☒	UZ	Uzbekistan
☒	KE	Kenya	☒	VN	Viet Nam
☒	KG	Kyrgyzstan	☒	YU	Yugoslavia
☒	KP	Democratic People's Republic of Korea	☒	ZA	South Africa
			☒	ZW	Zimbabwe
☒	KR	Republic of Korea	Check-boxes reserved for designating States which have become party to the PCT after issuance of this sheet:		
☒	KZ	Kazakhstan			
☒	LC	Saint Lucia	☒	AG	Antigua and Barbuda
☒	LK	Sri Lanka	☒	DZ	Algeria

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation (including fees) must reach the receiving Office within the 15-month time*

Supplemental Box *If the Supplemental Box is not used, this sheet need not be included in the request.*

*1. If, in any of the Boxes, **the space is insufficient** to furnish all the information: in such case, write "Continuation of Box No. ..." [indicate the number of the Box] and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:*

*(i) **if more than two persons are involved as applicants and/or inventors** and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;*

*(ii) if, in Box No. II or in any of the sub-boxes of Box No. III, the indication **"the States indicated in the Supplemental Box"** is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;*

*(iii) if, in Box No. II or in any of the sub-boxes of Box No. III, **the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America:** in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;*

*(iv) if, in addition to the agent(s) indicated in Box IV, there are **further agents**: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;*

*(v) if, in Box No. V, the name of any State (or OAPI) is accompanied by the indication **"patent of addition,"** or **"certificate of addition,"** or if, in Box No. V, the name of the United States of America is accompanied by an indication **"continuation"** or **"continuation-in-part"**: in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI) , the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;*

*(vi) if, in Box No. VI, there are **more than three earlier applications whose priority is claimed**: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI;*

*(vii) if, in Box No. VI, **the earlier application is an ARIPO application**: in such case, write "Continuation of Box No. VI", specify the number of the item corresponding to that earlier application and indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed.*

*2. If, with regard to the **precautionary designation statement** contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.*

*3. If the applicant claims, in respect of any designated Office, the benefits of provisions of the national law concerning **non-prejudicial disclosures or exceptions to lack of novelty**: in such case, write "Statement concerning non-prejudical disclosures or exceptions to lack of novelty" and furnish that statement below.*

Continuation of Box No. IV

NIKAIDO, David T.
MARMELSTEIN, Charles M.
ORAM, George E., Jr.
GOLDHUSH, Douglas H.
KITTS, Monica Chin
BERMAN, Richard J.
WONG, King L.
OZGU, Murat
GOLDIZEN, Bradley D.
NOLTE, N. Alexander
POULOS, James A., III
CARPENTER, Robert K.

all of:

Arent Fox Kintner Plotkin & Kahn, PLLC
1050 Connecticut Avenue, NW, Suite 600
Washington, DC 20036-5339 US

Telephone No: (202) 857-6000
Facsimile No: (202) 638-4810

Box No. VI PRIORITY CLAIM ☐ Further priority claims are indicated in the Supplemental Box.

Filing date of earlier application *(day/month/year)*	Number of earlier application	Where earlier application is: national application: country	regional application:* regional Office	international application: receiving Office
item (1) 30/04/99 30 April 1999	09/302,510	US		
item (2)				
item (3)				

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s): (1)

** Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):*

ISA/ EP

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority):*

Date *(day/month/year)* Number Country (or regional Office)

Box No. VIII CHECK LIST: LANGUAGE OF FILING

This international application contains the following **number of sheets:**

request	:	5
description (excluding sequence listing part)	:	25
claims	:	11
abstract	:	1
drawings	:	7
sequence listing part of description	:	
Total number of sheets	:	49

This international application is **accompanied** by the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☐ other *(specify):*

Figure of the drawings which should accompany the abstract: 8

Language of filing of the international application: English

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

MURRAY, Robert B.

For receiving Office use only

1. Date of actual receipt of the purported international application:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority (if two or more are competent): ISA/
6. ☐ Transmittal of search copy delayed until search fee is paid.

2. Drawings:
☐ received:
☐ not received:

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

This sheet is not pa... and does not count as a sheet of the international ...ication.

PCT

FEE CALCULATION SHEET

Annex to the Request

For receiving Office use only

International application No.

Date stamp of the receiving Office

Applicant's or agent's file reference: **F108064-00003**

Applicant: **Sabinsa Corporation, et al.**

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE . . . . . **240.00** T

2. SEARCH FEE . . . . . **990.00** S

International search to be carried out by **EP**

(If two or more International Searching Authorities are competent in relation to the international application, indicate the name of the Authority which is chosen to carry out the international search.)

3. INTERNATIONAL FEE

Basic Fee

The international application contains **49** sheets.

first 30 sheets **427.00** b1

19 remaining sheets x **$10.00** additional amount = **190.00** b2

Add amounts entered at b1 and b2 and enter total at B . . **617.00** B

Designation Fees

The international application contains **85** designations.

8 number of designation fees payable *(maximum 8)* x **92.00** amount of designation fee = **736.00** D

Add amounts entered at B and D and enter total at I . . . . . **1,353.00** I

(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the

4. FEE FOR PRIORITY DOCUMENT *(if applicable)* . . . . . **15.00** P

5. TOTAL FEES PAYABLE . . . . . **2,598.00** TOTAL

Add amounts entered at T, S, I and P, and enter total in the TOTAL box

☐ The designation fees are not paid at this time.

MODE OF PAYMENT

- ☐ authorization to charge deposit account (see below)
- ☐ bank draft
- ☐ coupons
- ☒ cheque
- ☐ cash
- ☐ other *(specify)*:
- ☐ postal money order
- ☐ revenue stamps

DEPOSIT ACCOUNT AUTHORIZATION *(this mode of payment may not be available at all receiving Offices)*

The RO/ **US**

- ☐ is hereby authorized to charge the total fees indicated above to my deposit account.
- ☒ *(this check-box may be marked only if the conditions for deposit accounts of the receiving Office so permit)* is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.
- ☐ is hereby authorized to charge the fee for preparation and transmittal of the priority document to the International Bureau of WIPO to my deposit account.

0123-00 Deposit Account No.

28/04/00 Date *(day/month/year)*

Signature

WO 00/66111
PCT/US00/08217

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

To:
MURRAY, Robert, B.
Arent Fox Kintner Plotkin & Kahn, PLLC
Suite 600
1050 Connecticut Avenue, N.W.
Washington, DC 20036-5339
ETATS-UNIS D'AMERIQUE

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

Date of mailing (day/month/year) 09 November 2000 (09.11.00)	
Applicant's or agent's file reference F108064-00003	**IMPORTANT NOTICE**

International application No.	**International filing date** (day/month/year)	**Priority date** (day/month/year)
PCT/US00/08217	28 April 2000 (28.04.00)	30 April 1999 (30.04.99)

Applicant
SABINSA CORPORATION et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AG,AU,DZ,KP,KR,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AE,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,CA,CH,CN,CR,CU,CZ,DE,DK,DM,EA,EE,EP,ES,FI,GB,GD, GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK,MN,MW,MX, NO,NZ,OA,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,UZ,VN,YU,ZA,ZW
   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   09 November 2000 (09.11.00) under No. WO 00/66111

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, **a demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer J. Zahra
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
F108064-0000		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 00/ 08217	28/04/2000	30/04/1999
Applicant		
SABINSA CORPORATION et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   COMPOSITIONS OF BOSWELLIC ACIDS DERIVED FROM BOSWELLIA SERRATA GUM RESIN, FOR TREATING LYMPHOPROLIFERATIVE AND AUTOIMMUNE CONDITIONS

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 8

   [X] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

14

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
F108064-0000		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/08217	28/04/2000	30/04/1999
International Patent Classification (IPC) or national classification and IPC A61K31/19		
Applicant SABINSA CORPORATION et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
30/11/2000	28.06.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Schnack, A Telephone No. +49 89 2399 8149

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/08217

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-25 as originally filed

Claims, No.:

1-85 as originally filed

Drawings, sheets:

1/4-4/4 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 45-66, 79-85.

because:

   ☒ the said international application, or the said claims Nos. 45-66, 79-85 relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

   Novelty (N) Yes: Claims none

	No:	Claims	1-85
Inventive step (IS)	Yes:	Claims	none
	No:	Claims	1-85
Industrial applicability (IA)	Yes:	Claims	1-44, 67-78 (for claims 45-66 and 79-85: see seperate sheet)
	No:	Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Reference is made to the following documents:

D1: EP 0 755 940
D2: EP 0 552 657
D3: Patent Abstracts of Japan, vol. 017, no. 100.
D4: WO 90 019 37
D5: Deutsche Apotheker Zeitung, (139/11) pp. 39-40
D6: Pharmazeutische Zeitung, (1997) 142/39, (pp. 1-20)
D7: Planta Medica, vol. 64, no. 4, 1998, pp. 328-331

Section III
Non-establishments of opinion:

Claims 45-66 and 79-85 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Section V
V.1. Novelty
Remarks under Article 33(2) PCT:

Compositions comprising the present boswellic acids and uses thereof are already known, (see at least D1-D4, the passages mentioned in the search report). Thus, the subject matter according to present claims 1-44 appears to lack novelty with respect to these documents.

The present methods for obtaining the present boswellic acids are also known from D1, (see D1, claims 3-11). Thus, the subject matter of present claims 67-78 appears to lack novelty with respect to D1. Also the extracts and powders according to D2-D4 must have been obtained by a process at least very similar to the present process.

The present medical uses, (inhibition of DNA, RNA or protein synthesis, autoimmune diseases, cancer treatment and lymphoproliferative diseases), of the present

compounds are also known, (see D5, the entire document, which discloses the therapeutic effect in cancer treatment, D6, the passages mentioned in the search report, which discloses cancer treatment, rheumatoid arthritis and inhibition of DNA synthesis, and D7, which discloses treatment of leukemia and inhibition of DNA synthesis). Thus, the subject matter according to present claims 45-66 and 79-85 appears to lack novelty with resect to these documents.

V.2. Inventive step

Remarks under Article 33(3) PCT:

It is not considered to be inventive to arbitrary select specific amounts of the four known active components in a composition for treating diseases known to be treatable with the present compounds.

No other inventive features can be seen in the present subject matter.

V.3 Industrial applicability

Remarks under Article 33(4) PCT:

For the assessment of the present claims 45-66 and 79-85 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Section VIII

The present claim are inconcise contrary to Article 6 PCT, because there are too many independent claims: (claims 1, 9, 14, 19 and 24 all relate to compositions comprising one or more of the active components and claims 45, 48, 51, 55, 59, 63, 79, 82, 83, 84 and 85 all relate to treatment of different diseases). This number of independent claims in the same category is considered to be far more than acceptable under Article 6 PCT.

Usually only one independent claim in each category is considered allowable under Article 6 PCT, unless special circumstances are present, which do not appear to be the case presently.